

COVID-19 and Long Covid: Organs Damage and Dysfunctions, and Implications for Clinical Course

Subject Category: Clinical Virology

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Submitted: 18 August 2021 | **Approved:** 11 October 2021 | **Published:** 18 October 2021

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DOI: <https://dx.doi.org/10.29328/ebook1005>

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Table of Contents - 7 Chapters

Sl No	Chapters	Title	Pages
1	Preface	COVID-19 and Long Covid as Multi-organ Involvement and Multi-system Disease	003-008
2	Chapter 1	The Saga of Erratic Immune Response, Waning Immunity and Immune System Failure	009-020
3	Chapter 2	Pulmonary Involvement in COVID-19 and 'Long Covid': The Morbidity, Complications and Sequelae	021-036
4	Chapter 3	Exploring Cardiovascular Morbidity, Complications and Sequelae	037-053
5	Chapter 4	Involvement of Gastrointestinal and Hepato-Biliary System in COVID-19 and Long Covid	054-071
6	Chapter 5	Neurological and psychiatric effects of COVID-19 and Long Covid	072-088
7	Chapter 6	Involvement of Kidneys and Endocrine System, and Skin in COVID-19 and Long Covid	089-105
8	Chapter 7	Exploring Etiopathophysiological Links and Clinical Course of Long Covid	106-116
9	Postscript	The Ongoing Pandemic: Compromised Health, and Confined and Restricted Human Life	117-122
10	Acknowledgement		123-123

Preface: COVID-19 and Long Covid as Multi-organ Involvement and Multi-system Disease

The virus infection, the disease and post-disease

Like any other infectious disease, the prognosis of COVID-19 is influenced by infecting agent, the SARS-CoV-2 virus load and the extent of organs affliction and damage. COVID-19 having a propensity for multiorgan involvement carries an adverse prognosis during the clinical course as well as later during the post-recovery period persisting as Long Covid. The direct cytopathic effects of SARS-CoV-2 virus and the erratic and hyper-inflammatory response lead to tissue injury in various organs coupled with physiological dysfunctions and complications. In fact, the multi-system manifestations of COVID-19 are caused by a combination of specific host defence responses with associated inflammatory activity and vascular involvement with coagulopathy and a distinct propensity to develop thromboembolic complications. Simultaneously, comorbidities such as diabetes, hypertension and cardiovascular diseases influence the disease severity and mortality.

All age groups are susceptible to SARS-CoV-2 infection and advancing age and comorbidities are risk factors for infection, severe disease, and adverse prognosis. The routes of transmission of SARS-CoV-2 infection are through respiratory droplets released while talking, coughing, or sneezing; via aerosol as the virus is known to remain suspended in air specially in confined places; through mucosal membrane contact with fomites, and likely via faecal-oral transmission given the detection of viral RNA in stools in those with or without symptoms related to the gastrointestinal (GI) system as it has an abundant ACE2 expression. Following infection, viral shedding occurs in all those infected including asymptomatic individuals. There is a wide spectrum of clinical manifestations of COVID-19 ranging from asymptomatic or pauci-symptomatic forms to severe viral pneumonia with ARDS, multiorgan dysfunctions, septicaemia, and shock, and death.

The assessment of illness severity at admission through evaluation of the Sequential Organ Failure Assessment (SOFA) and Quick Sequential Organ Failure Assessment (qSOFA) scoring systems is helpful in identifying the COVID-19 patients with poor prognosis and a high risk for adverse outcome. Liu, et al. have documented that a SOFA score of ≥ 3 or a qSOFA score of ≥ 1 was associated with high mortality in severely ill COVID-19 patients [1]. As such, the SOFA score is prognostically superior to qSOFA in this setting, attributable to inclusion of higher number of clinical parameters and variables, which facilitates an accurate patient stratification. The parameters include mean arterial pressure, platelets count, bilirubin, creatinine, PaO_2 , FiO_2 , and D-dimer levels on admission [2]. The pathogenic mechanisms underlying alterations in these clinical correlates in COVID-19 patients are diverse.

Organs involvement in COVID-19 and Long Covid

Though primarily a respiratory viral disease, COVID-19 is a multi-organ and multi-system disease in a true sense. While it presents with common-cold-like symptoms in mild cases, the severe illness is characterised by multiorgan dysfunction and failure. The multi-organ involvement in COVID-19 can potentially lead to pneumonia and ARDS, acute liver dysfunction, acute kidney injury, cardiovascular disease, and a wide spectrum of gastro-intestinal (GI), neurological endocrinal, and haematological abnormalities (Figure 1).

The abundant expression of ACE2, the receptor for SARS-CoV2 in the respiratory, cardiovascular, GI, and endocrinal organs is partly responsible. The other factors include direct cytopathic injury, aberrant and over-active immune system manifesting as increased levels of inflammatory mediators and cytokine storm syndrome, and complications like endothelial dysfunction, coagulation disorders and thrombotic abnormalities.

The respiratory system: The mild illness in COVID-19 resembles upper respiratory tract infection with nonspecific symptoms such as fever, headache, sore throat, cough (with or without sputum), anorexia, malaise, fatigue, muscle pain, and fatigue. Non-severe pneumonia may occur with moderate symptoms and without requirement for supplemental oxygen. Whereas severe pneumonia presents with fever, chest pain and respiratory discomfort with respiratory rate > 30 breaths/min and reduced SpO_2 on room air. The severe pneumonia may lead to acute respiratory distress syndrome (ARDS) of varying severity from mild to moderate to severe ARDS. The COVID-19 pneumonia has been categorized as

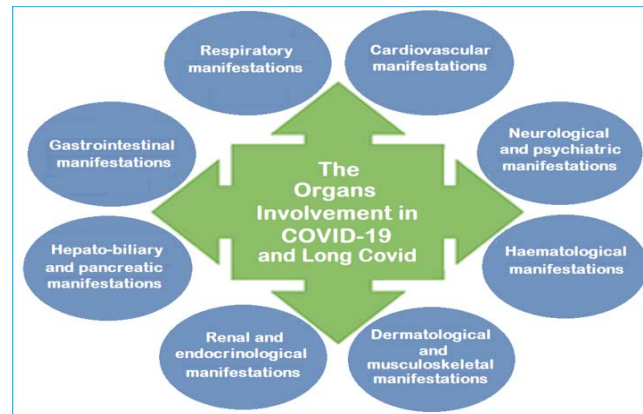


Figure 1: The respiratory, cardiovascular, gastrointestinal and hepato-biliary, neurological and psychiatric, renal and endocrinological, haematological, musculoskeletal, and dermatological manifestations in COVID-19 and Long Covid.

type L with low lung elastance, low recruitability, and a poor response to positive end-expiratory pressure (PEEP) and type H as having high lung elastance, extensive consolidations on CT imaging, and significant response to higher PEEP [3]. In general, in about 80% of the COVID-19 patients, the respiratory involvement is mild and restricted to the upper airways, while the remaining 20% of the patients go on to develop pulmonary infiltrates as the virus invades the alveoli and infects the peripheral and subpleural units [4].

The cardiovascular system: The patients with existing cardiovascular disease (CVD) are at a greater risk of suffering from severe COVID-19 and poor prognosis, whereas between 5% to 25% of the hospitalized COVID-19 patients show evidence of myocardial involvement in form of myocardial infarction, myocarditis, and cardiomyopathy without a prior diagnosis of hypertension or CVD [5]. There are multiple proposed aetiologies for adverse cardiovascular involvement and include the viral cytopathic effect via ACE2, a hyperinflammatory state, downregulation of ACE2 leading to pro-inflammatory and pro-fibrotic milieu, increased procoagulant activity, and increased cardiac physiologic demand. Given the hyperinflammatory and hypercoagulable state and increased metabolic demand COVID-19 patients may be at increased risk for acute myocardial ischaemia and infarction [6]. Elevated troponins have been found in COVID-19 patients denoting myocardial hypoxia and ischaemia or myocardial injury, whereas electrocardiogram (ECG) may show a range of findings mimicking ACS and echocardiography may show global dysfunction with myocarditis. The ECG and echocardiographic abnormalities are markers of severity in COVID-19 patients and correlated with adverse outcomes [7].

The neurological system: Neurologic manifestations occur in more than one-third of patients hospitalized with COVID-19 [8]. Mao, et al. reported that in their cohort 36.4% of COVID-19 had neurologic manifestations [9]. The potential mechanisms of neurologic injury from COVID-19 include direct viral damage of nervous tissue, injury resulting from the excessive inflammatory response, erratic and hyper-immune response, and injury resulting from the effects of systemic illness. In fact, most COVID-related neurologic complications in critically ill patients fall into the latter category. A variety of neurological manifestations like headache, hyposmia, and hypogeusia are common, whereas the patients with severe COVID-19 are more likely to have neurological complications including delirium, encephalopathy, acute cerebrovascular disease, and other critical manifestations including skeletal muscle injury and myopathy [10]. On the serious side, meningoencephalitis, haemorrhagic encephalopathy, and acute necrotising encephalopathy may occur.

The gastrointestinal system: The incidence of GI involvement ranges from 12% - 61% in patients with COVID-19 [11]. The commonly reported GI symptoms are diarrhoea, nausea, vomiting, and abdominal pain, and may be the sole presenting complaint in many cases. The hepatic injury occurs in 15% to 65% of COVID-19 patients ranging from mild and transient, the most common finding being abnormal transaminase levels, to severe damage in patients with severe COVID-19 infection [12]. The virus, SARS-CoV-2 has a tropism for the GI tract due to abundant presence of ACE2 in GI epithelial cells and the SARS-CoV-2 RNA is readily detected in stool specimens, even when respiratory samples are negative [13]. The mechanisms of liver injury include viral cytopathic effect, immune-related injury, and drug

hepatotoxicity. In patients with transaminitis, the medications with potential hepatotoxicity such as acetaminophen, statins, and hydroxychloroquine, should be used with caution. The patients with severe COVID-19 are at high risk of hepatobiliary, hypomotility, and ischemic GI complications due to small vessel thrombosis and viral enteroneuropathy [14].

The renal system: The acute kidney injury (AKI), the abrupt loss of kidney function, is common in COVID-19 patients and the severity of AKI has been linked to adverse outcomes [15]. The alterations in renal function indicators such as blood urea, serum creatinine, proteinuria, and haematuria are predictors of AKI. The AKI occurs in 0.5% - 15% of hospitalized COVID-19 patients, and up to 23% of critically ill patients. The median onset of AKI from hospitalization ranges from 7 to 15 days, and it is an independent risk factor for morbidity and mortality [16]. The AKI is thought to occur through several proposed mechanisms, including intrinsic cellular injury by direct viral invasion of the renal tissue, acute tubular necrosis induced by septicaemia, hypoxia, hypovolemic state, and rhabdomyolysis. The management of AKI in COVID-19 patients must account for extent of renal damage. The renal replacement therapy (RRT) may be required in critically ill COVID-19 patients with AKI. The electrolyte abnormalities, such as hyperkalemia, hyponatremia, and hypernatremia, and metabolic acidosis may occur along with renal involvement and dysfunction.

The endocrine system: While the effects of SARS-CoV-2 infection on the endocrine system remain largely unknown, given the expression of ACE2 in the majority of endocrine glands, dysfunction of various endocrine organs may occur in patients with severe COVID-19. In fact, a range of endocrine manifestations have been seen in COVID-19 patients without a pre-existing endocrine disease. The hospitalised COVID-19 patients commonly exhibit the abnormalities of glucose metabolism, such as worsened hyperglycemia, euglycemic ketosis, and diabetic ketoacidosis. Further, infection can cause new-onset diabetes [17]. Among exocrine pancreatic features, while pancreatitis is uncommon, elevated lipase or amylase have been documented in patients with COVID-19. In general, the diabetic patients are at higher risk for SARS-CoV-2 infection than the general population and more likely to have a severe disease due to compromised innate immunity and downregulated ACE2 levels [18]. Obesity is associated with severe COVID-19 due to ACE2 expression in adipose tissue and pro-inflammatory milieu. The SARS-CoV-2 infection affects the hypothalamus–pituitary axis either directly or via immune-mediated hypophysitis leading to central hypocortisolism and diabetes insipidus. The patients with severe COVID-19 are prone to develop critical illness-related corticosteroid insufficiency. Finally, COVID-19 may lead to subacute thyroiditis and other thyroid disorders.

The musculoskeletal system: Myalgias are a common presenting symptom of COVID-19 and occur in more than one-third of patients and elevated creatinine kinase levels are prevalent in hospitalized patients and in patients with severe disease [19]. There is a possibility that myositis and rhabdomyolysis, the potential complication of COVID-19, are more common than reported due to muscle pains being a common symptom during the illness as well as creatine kinase and myoglobin levels are not being routinely tested. In a recent study, the incidence of rhabdomyolysis was 16.9% among all admitted COVID-19 patients [20]. In addition, the critically ill COVID-19 patients are at risk of developing myopathy and neuropathy due to prolonged immobility, systemic inflammation, corticosteroids, and the use of neuromuscular blocking agents. There has been recommended an early mobilization and initiation of physical therapy in these patients to ensure the best functional outcome [21].

The dermatologic manifestations: A variety of cutaneous manifestations such as erythematous rash, generalized urticaria, and chickenpox-like lesions have been described in COVID-19 and occur in up to 36% of the patients [22]. The skin manifestations may occur even before the onset of usual COVID-19 symptoms. There has not been established an association between cutaneous manifestations and COVID-19 severity, but dermatologic manifestations may reveal micro-thrombosis, hypercoagulability, and disseminated intravascular coagulation (DIC). The urticarial eruptions are typically consistent histologically with a viral exanthem. Livedo reticularis, a cutaneous manifestation is associated with DIC, whereas acrocyanosis and limb ischemia have been described in a cohort of critically ill patients with elevated D-dimer, fibrinogen, and fibrinogen degradation products [23]. The chilblains-like lesions, are erythematous areas on the feet, described as ‘Covid toes,’ may represent endotheliitis secondary to systemic COVID-19. A purpuric rash in patients with severe COVID-19 is probably caused localization of SARS-CoV-2 spike glycoprotein causing complement activation and thrombogenic vasculopathy.

The haematological system: The COVID-19 patients present with several haematological abnormalities and thromboembolic complications. In general, leukocytosis (especially neutrophilia), lymphopenia, and thrombocytopenia are common and associated with adverse clinical course [24]. Simultaneously, the immune response to the virus infection is associated with increased circulating levels of pro-inflammatory cytokines, including tumor necrosis factor (TNF)- α , interleukins, granulocyte-colony stimulating factor, and chemokines. The hyper-inflammatory milieu combined with hypercoagulability carries the risk of venous thromboembolism and adverse outcomes [25]. Thus, the COVID-19 patients often present with both impaired haemostasis as well as thrombotic events [26]. Elevated fibrinogen and D-dimer levels are the most common coagulopathy seen in hospitalized COVID-19 patients. With the deranged coagulation cascade, DIC is another serious complication of COVID-19. The patients with COVID-19 are also at an increased risk of venous thromboembolic (VTE) disease and the use of anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin may improve clinical outcomes. Further, post-hospital discharge VTE prophylaxis may be considered in these patients depending on a case-by-case basis [27].

The immunological system: The immune response is understandably the key determinant of the susceptibility to SARS-CoV-2 infection and severity of COVID-19 [28]. While weak immune system can increase the risk of acquiring SARS-CoV-2 infection and cause severe disease, the hyperinflammatory response to the infection is responsible for various complications by triggering organs involvement and damage [29]. The erratic immune response leads to the surge in inflammatory parameters like IL-2, IL-7, granulocyte-colony stimulating factor, interferon- γ inducible protein, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- α , and tumor necrosis factor- α leading to an imbalanced and hyper-immune response responsible for cytokine storm. Throughout the disease course, there is required serial monitoring of lymphocyte count dynamics and inflammatory indices such as lactate dehydrogenase, C-reactive protein, and interleukin-6, for prognostic evaluation and measures for timely intervention.

The clinical manifestations, course, and fallouts

Given the world-wide viral pandemic with considerable morbidity and mortality, and post-recovery manifestations, the COVID-19 is an enigma. To simplify, the disease course can be divided into three distinct stages, beginning with acquiring the infection - Stage 1; which can sometimes progress to pulmonary involvement - Stage 2, with or without hypoxemia; and thereafter less frequently to systemic inflammation - Stage 3 [30]. The Stage 1 is the mild phase when the virus multiplies and establishes itself in the host tissues, predominantly in the respiratory tract. In Stage 2, there occurs viral multiplication and localized inflammation in the lungs, whereas the Stage 3 is marked by extra-pulmonary systemic hyperinflammation manifestations. The outcomes from the Stage 3 are often adverse. The Stage 3 is followed by recovery which may be afflicted by Long Covid manifestations for a variable period. There are certain comorbid conditions which worsen the outcome and include advanced age, hypertension, diabetes, coronary artery disease, chronic lung disease, and malignancies [31]. The studies have also documented variations in outcomes due to a dysregulated and hyperactive immune response.

Based on retrospective data from various studies, it seems that the progression of the disease can be predicted. From the therapeutic point, it appears that apart from exploring an effective anti-viral therapy, an important modality may be to down-regulate the inflammatory markers to limit the organs damage in COVID-19 [32]. In fact, the therapeutics of COVID-19 is still evolving, and recommendations may change, as apparent from the incredible volume and speed at which data is being published about the epidemiology, clinical manifestations, and treatment of COVID-19 [33]. This e-Book, the third* in the series, aims to deal with the subject in a modest but judicious way about the epidemiological, clinical, and therapeutic aspects of COVID-19 and Long Covid and may be useful for researchers, clinicians, and enlightened readers with interest in biological sciences.

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Chapter 1: The Saga of Erratic Immune Response, Waning Immunity and Immune System Failure

Background

Introduction - evolution of SARS-CoV-2 variants: With the unrestrained pandemic for over last one-and-half year, SARS-CoV-2 seems to have adapted to its habitat, the human host, through mutations that facilitate its replication and transmission. The G variant incorporating D614G mutation, potentially more transmissible than the ancestral virus arose during January 2020 and spread widely. Since then, various SARS-CoV-2 variants of concern (VOCs) and variants of interest (VOIs) with higher infectivity or virulence or both, have evolved on the background of G variant, and spread widely.

SARS-CoV-2 infection and the immunodynamics: As the virus becomes more transmissible, its lethality may drop. Apart from the humoral immunity, T-cell recognition from a previous SARS-CoV-2 infection or vaccination may modify the disease transmission correlates and its clinical manifestations. On the other hand, the immunity generated may reduce probability of re-infection as well as limit evolution of adaptive mutations, and emergence of highly infectious and immune-escape variants. There are complex issues related to the SARS-CoV-2 evolutionary dynamics and host's immunodynamics.

Trending etiopathoimmunological correlates: The evolution potential of SARS-CoV-2 is limited because of proofreading function of nsp14. The S protein mutations affect transmissibility, virulence, and vaccine efficacy. The D614G mutation in G variant with higher infectivity has turned the Chinese epidemic into a pandemic. Other SARS-CoV-2 variants, such as Alpha, Beta, Gamma, and Delta seem to have evolved as result of adaptation to selective pressures during periods of prolonged infections and subsequent transmission. Further, there is issue of convergent association of mutations.

Basics of immunity and immune system failure: The nature of the immune response after natural SARS-CoV-2 infection is variable and diverse. There are pre-existing neutralizing antibodies and sensitized T cells elicited during previous infection with seasonal CoVs influencing the disease susceptibility and course. The virus has evolved adaptive mechanisms to reduce its exposure to IFN-I and there are issues related to erratic and overactive immune response. The altered neutralizing epitopes in the S protein in SARS-CoV-2 variants modify the immune landscapes and clinical manifestations.

Conclusion: Current scenarios and prospects: Presently, the SARS-CoV-2 infection is widespread with multiple evolving infectious variants. There is probability of its transition from epidemic to endemic phase in due course manifesting as a mild disease especially in the younger population. Conversely, the pandemic may continue with enhanced disease severity due to evolving variants, expanded infection pool, and changing immunity landscape. There is need to plan for the transition and continued circulation of the virus during the endemic phase or continuing pandemic for indefinite period.

Introduction – emerging SARS-CoV-2 variants

The pandemic and evolution of d614g or g variant

The mutation process is a natural characteristic of the lifespan of a virus. Over time, the viruses replicate and mutate into more transmissible but less virulent forms to persist inside the host and extend their lifespan. Apparently, the transmissibility and virulence may have an inversely proportional relationship, and in general, the viral mutations lead to higher transmissibility and lower virulence. In other words, with ongoing evolution a virus tends to become more transmissible but less lethal. A particular variant may have higher transmission potential if the infected hosts are shedding more virus. The natural selection appears to act on variation in viral transmission potential and not variation in virulence, per se. There is a probability, though, the virus may evolve to become more virulent, causing more severe disease and host mortality. However, a more severe infection may reduce contact rates of infected individuals, limiting the opportunity for viral transmission.

Over last one-and-half year, SARS-CoV-2 seems to have adapted to its habitat, the human host, through mutations that

facilitate its replication and transmission [1]. One widespread and more transmissible variant than the ancestral virus is D614G or G variant in which aspartic acid (D) had been replaced with glycine (G) at amino acid position 614 in the S protein (Figure 1).

There is likelihood that the G variant arose during January 2020 in early phase of epidemic in China and became dominant worldwide. The D-to-G substitution appears to have resulted in more efficient infection, replication, and enhanced transmission. The observed increased frequency of infection with SARS-CoV-2 G variant is consistent with the selective advantage for the virus. Further, the D614G form is associated with higher viral loads and younger patient age, though there is no association of with increased severity of infection [2]. In fact, the S protein is made up of three smaller peptides which bind to the ACE2 receptors. The peptides are in open or closed orientation, with the open orientation facilitating their binding with the receptors. The D614 G mutation seems to relax the connexions between the peptides and favouring the receptor bonding and cellular internalization.

The D614G mutation in the S glycoprotein of SARS-CoV-2 was first identified in virus sequences in several Chinese provinces in late January, and later detected in early March 2020 at other places. By June 2020, the G variant replaced the ancestral virus to become the dominant form globally [3]. Further, the mutation seems to have arisen independently and simultaneously across multiple geographic regions, which is suggestive of natural selection and an adaptive benefit of D614G for the virus. As observed, the mutation leads to increased infectivity and transmission than the ancestral virus with 614D but neither causes a more severe illness nor impacts the effectiveness of lab tests, therapies, and vaccines (2). The G variant, which originally emerged in China, has subsequently spread around the world. The D614G's spike protein sequence has been used to develop the vaccines in use presently.

Going through the progression of the SAR-CoV-2 infection, it originally started with the L strain that appeared in Wuhan in December 2019. Its first mutation, the S strain appeared at the beginning of 2020, which mutated to G strain by mid-January 2020. The G strain has mutated further into sub-strains GR and GH at the end of February 2020. Presently, the G, GR and GH forms are by far the most widespread and encompass for about 74% of all gene sequences henceforth analysed [4].

The ongoing evolution of SARS-CoV-2 virus

Various SARS-CoV-2 variants of concern (VOCs) have evolved on the background of D614G mutation which arose during January 2020 and spread widely replacing the ancestral virus. During September-October 2020, a new SARS-CoV-2 lineage, B.1.1.7 (Alpha variant), having substantial fitness advantages over other circulating lineages, rapidly spread from the UK to various countries around the globe. More recently, the SARS-CoV-2 lineage, B.1.617.2 was first detected in India in late 2020 (named Delta variant by WHO later on 31 May 2021), has led to widespread resurgence, and subsequently has spread to other countries. The Delta variant has mutations such as the substitutions T478K, P681R and L452R in the S protein, which lead to higher transmissibility and reduced neutralization by antibodies for previously circulating variants of the COVID-19 virus [5]. Further, its secondary attack rates are stated to be 51–67% higher than the Alpha variant, apart from the fatality rate being about 1.9% higher than the Alpha variant [6]. Other VOCs are Beta (B.1.351), Gamma (P.1), and Alpha (B.1.1.7) with E484K. In addition, there are certain variants of interest, such as Epsilon, Zeta, Eta, Theta, Iota, and Kappa. The virus SARS-CoV-2, thus, has the capacity to evolve into more efficient variants (Figure 2).

As SARS-CoV-2 continues to spread, the new variants are developing under evolutionary pressures such as host immunity as the result of infection or vaccination, chronicity of SARS-CoV-2 infection, partial and erratic immunity, and

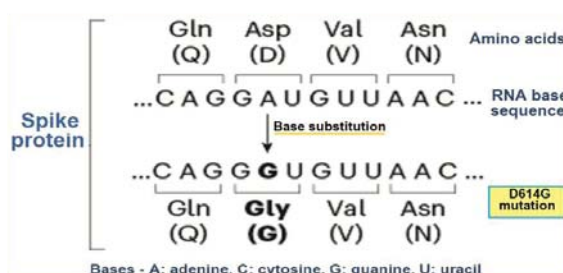


Figure 1: The evolution of D614G or the G variant.

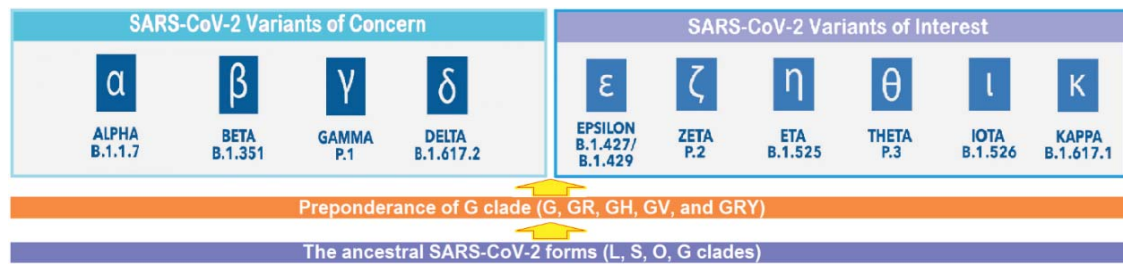


Figure 2: The ongoing evolution of SARS-CoV-2: From L, S, O and G clades to G, GR, GH, and other G clades, and further evolution from various G clades to Variants of Concern (VOCs) and Variants of Interest (VOIs).

perhaps genetic variations in various races and human population groups. There is emerging evidence to suggest that some SARS-CoV-2 variants may carry enhanced antigenicity, leading to likely build-up of differential herd immunity among population groups through natural infection or vaccination. On the other hand, the emergent SARS-CoV-2 lineages may potentially escape vaccine or natural immunity. Additionally, carrier state for indefinite period in those exposed to infection and animal reservoirs may develop to complicate the dynamics of SARS-CoV-2 evolution and adaptation.

SARS-CoV-2 and host immunodynamics

Viral evolution, transmissibility and virulence

In general, as the virus becomes more transmissible, its lethality may drop. Further, there is evidence to show that the T-cell recognition from a previous SARS-CoV-2 infection or vaccination may be able to deal partially with the new variants in terms of modified disease transmission and clinical manifestations. Thus, it is being presumed that the neutralizing effect of T-cells within the population as well as the diminishing lethality of the virus may lower down the infection rate in due course. There are reasons to believe that intermediate levels of immunity generated through natural infection or vaccination may reduce the probability of infection as well as limit the evolution of adaptive mutations by restricting the viral population size within vaccinated hosts. Furthermore, viral loads are lower in infections 12 to 28 days after a single dose of vaccine than in unvaccinated individuals, indicating diminished likelihood of transmission by vaccinated individuals [7]. Similarly, the vaccination is likely to slow the viral evolution. Thus, reducing numbers of infections through vaccination could reduce the chances for variants to be generated, selected, and transmitted [8]. In fact, there is likelihood of emergence rate of immune-escape variants being mitigated by reduced opportunities of the confluence of mutation, selection, and transmission following widespread vaccination.

But the issues related to evolutionary dynamics of SARS-CoV-2 as well as host's immunodynamics are intricate and full of uncertainties. There is possibility that the SARS-CoV-2 vaccine dosing regimens generating intermediate levels of immunity could accelerate the emergence of new variants, especially the immune-escape variants, capable of escaping immunity wholly or partially induced by prior infection or vaccination [9]. In fact, a noteworthy hypothesis being advanced asserts that such variants may arise through *de novo* mutation and selection in partially immune hosts due to the weak immune response following infection or vaccination. This conjecture is being challenged as the transmission of SARS-CoV-2 virus typically takes place in the early stage of infection following relatively few cycles of replication [10]. Further, there may not be adequate prospects for adaptive mutants to be generated in a frequency that may lead to onward transmission, and the intermediate levels of immunity may also sufficiently restrict viral replication and thus limit adaptive mutations [11].

It has been observed that those infected with high viral load generally have one or few within-host variants. In other words, in most of SARS-CoV-2 infection, there is low levels of within-host diversity when viral loads are high. Further, the major variant is typically transmitted from the host, whereas the minor variants lost. Only sporadically, the minor variant is transmitted, or multiple variants are transmitted, leading to a mixed infection from SARS-CoV-2 variants. The virulent variant is indicated by severity of the disease as well as the ensuing mortality rate, it can cause. In general, if the virus becomes more transmissible, its lethality may drop. But in this respect, the D614G variant having increased transmissibility, spread globally during the first year of the pandemic with no obvious drop in its virulence. Further, the current VOCs, B.1.1.7 lineage has an estimated transmission advantage of ~50% and B.1.617.2 more transmissible than the former, manifest a higher virulence than the ancestral lineages. In addition, they are presumed to have acquired a

decreased sensitivity to natural and/or vaccine-acquired immunity similar to the B.1.351 and P.1 variants, underlining the fact that the evolving SARS-CoV-2 may behave in a complex way with new mutations or combinations of mutations conferring selective advantages to the virus.

Viral phylogenics and epidemiological dynamics

Through identifying SNPs, the viral phylogenics can be used to evaluate viral emergence, characterize the geographical spread, reconstruct epidemiological dynamics, and identify instances of adaptation. As estimated, the SARS-CoV-2 virus evolves at a rate of $\sim 1.1 \times 10^{-3}$ substitutions per site per year, which corresponds to one substitution every ~ 11 days, and has the most recent common ancestor (TMRCA) around late November 2019 [12]. The phylodynamic analyses can also give information about the virus spread, both spatially and temporally, and allow to identify the viruses circulating in a region as well as new virus introductions. In addition, the phylodynamic techniques may indicate the rate of viral spread through a host population and identify occurrence of viral adaptations. The number of available SARS-CoV-2 genomic sequences is enormous. These are often reported without exact sampling location data because of certain privacy issues. However, viral dynamics may be heterogeneous even within and between geographically close locations. Furthermore, the travel related issues complicate the phylodynamic data. Despite these challenges, a huge reliable SARS-CoV-2 sequence data is available on GISAID's EpiCov database and on other platforms such as Nextstrain and Microreact. Because of their potential phenotypic effects, evolution of genomic insertions, deletions, and recombinants are of paramount significance and need to be monitored.

The viruses evolve as a result of mutations and natural selection for favourable traits such as more efficient viral replication, transmission, and evasion of host defences. In general, the viral adaptations take place through the evolution of novel viral traits such as immune escape through genetic variation. The latter occurs through nucleotide substitutions, misincorporations, insertions or deletions. Apart from this, the recombinations are common in CoVs during replication and give rise to new SARS-CoV-2 lineages. But the diversity of SARS-CoV-2 is limited because of proofreading function of the 3'-5' exonuclease nsp14. Thus, the vaccines based on a single sequence of the viral S protein are likely to generate an immune response protective to various circulating variants. However, the newer variants of SARS-CoV-2 with mutations in S protein have emerged, posing potential challenges for vaccination and antibody-based therapies. The continuing pandemic and unprecedented spread of SARS-CoV-2 may lead to the possibility for accumulation of additional consequential mutations in S protein and throughout the viral genome [13].

Trending etiopathoimmunological correlates

Intra-host diversity and onward transmission

The SARS-CoV-2 shares high sequence homology with SARS-CoV both in genomic structure and host receptor preference. Whereas SARS-CoV-2 and the common cold human coronavirus, HCoV-NL63, though both recognize ACE2 as the host cell receptor, have major sequence and structural differences in the receptor-binding domain (RBD) of S protein. This diversity indicates that CoVs can potentially tolerate changes in both sequence and structure without substantial loss of function. The S protein has two subunits, S1 which contains an amino (N)-terminal domain (NTD) and receptor-binding domain (RBD), and the subunit S2 which mediates virus-host cell fusion. The antibody-neutralizing epitopes are scattered throughout S protein but are mostly concentrated in the RBD. As such, the evolution potential of SARS-CoV-2 is limited because of proofreading function of nsp14. The understanding about the individual phenotypic effects of the S1 mutations is emerging, and it has been noted that substitutions and deletions in S1 can affect transmissibility (Tr), vaccine efficacy (Ef), and virulence (Vi). The first notable evolutionary event was the D614G (Asp⁶¹⁴→Gly) substitution, which increased the ACE2 affinity, leading to higher infectivity and transmissibility of the G variant.

Further, the substitution at position Asn⁵⁰¹ with Thr or Phe increases affinity for ACE2 binding [14]. The substitution at position 452, a leucine-to-arginine substitution (L452R), confers higher affinity of the S protein for the ACE2 receptor and decreased recognition by immune system. Whereas the substitution at position 681, a proline-to-arginine substitution (P681R), facilitates cleavage of the S precursor protein to the active S1/S2 configuration and, thus, boosts cell-level infectivity. The variants may have reduced sensitivity to neutralizing antibodies that bind to the RBD because of triple substitutions of key amino acids, Lys417, Glu484, and Asn501, in the RBD at the ACE2-binding interface or the NTD. It is possible that there is a convergent association of mutations. The mutations that reduce neutralizing antibody binding, such as E484K, may require compensatory mutations that restore infectivity, such as N501Y, as is the case in the B.1.351

and P.1 lineages. Similar situation occurs in B.1.1.7^[K] or Alpha^[K] lineage, where E484K is present with N501Y. The role of compensatory mutations is also supported by the emerging B.1.525 lineage that has both E484K and $\Delta 69-70$ leading to reduced antibody sensitivity and compensatory increase in infectivity, respectively.

The diversity of SARS-CoV-2 is limited because of proofreading function of the 3'-5' exonuclease nsp14. Albeit, the proofreading capacity of nsp14 is limited to point mutations and it cannot repair other greater alterations such as deletion, insertion, recombination or misincorporation. Thus, significant intra-host evolution of SARS-CoV-2 can occur as reported various case studies in some patients with protracted infection due to impaired immunity [15,16]. These patients had up to fivefold reduced neutralization sensitivity to convalescent plasma (CP) and/or monoclonal antibody therapy, in addition to shedding high titers of SARS-CoV-2 and having active SARS-CoV-2 infection for an average of 115 days before clearing the infection or succumbing to COVID-19 [17,18]. These case studies in immunocompromised patients have documented the deletions of amino acids 69 to 70 ($\Delta 69-70$), $\Delta 141-144$, or $\Delta 242-248$ in S1; the N501T (Asn⁵⁰¹→Thr) or N501Y (Asn⁵⁰¹→Tyr) mutations; and the E484K (Glu⁴⁸⁴→Lys) and Q493K (Gln⁴⁹³→Lys) mutations in the RBD. There have been found various deletions in the amino (N)-terminal domain (NTD) of S1 in B.1.1.7 and B.1.351. In addition, other mutations in these variants include K417N, E484K, and N501Y. It is noteworthy that these reports preceded the detection of three major circulating variants—B.1.1.7, B.1.351, and P.1, which contain at least eight single, nonsynonymous nucleotide changes, including E484K, N501Y, and/or K417N (Lys⁴¹⁷→Asn) in the RBD [19]. Occasionally, SARS-CoV-2 virus can evolve into multiple distinct lineages within the same infected individual [20].

The complex process of immune response

Several studies suggest that the major circulating variants, such as B.1.351, P.1, and B.1.1.7 lineages, and probably B.1.617.2 lineage have reduced neutralizing sensitivity to convalescent plasma and plasma from recently vaccinated individuals [21,22]. Though, the reduced antibody sensitivity against these variants do not invariably prove that a vaccine is not effective, still the recent data suggests that certain vaccines may be especially less protective against the B.1.351 variant [23]. Further, there is growing concern for the emergence of immune escape mutants in a protracted SARS-CoV-2 infection. Similarly, the partial roll-out and incomplete immunization of individuals leading to suboptimal titers of neutralizing antibody could also promote evolution of escape variants. On the other hand, halting the spread of SARS-CoV-2 through a coordinated and comprehensive vaccination programme and prevention strategies like masking and social distancing are likely to prevent the evolution of immune escape variants.

The immune response following SARS-CoV-2 infection or COVID-19 vaccination is a complex process (Figure 3). The

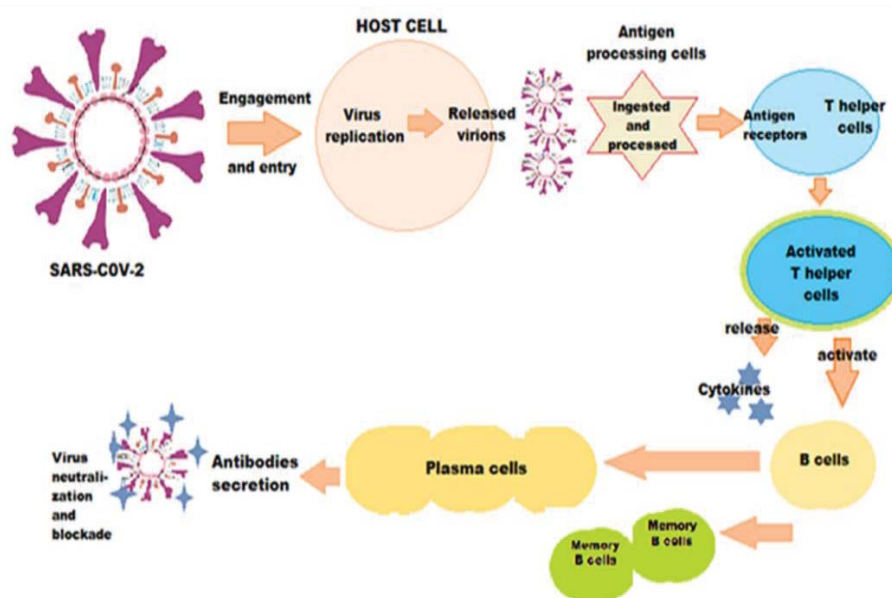


Figure 3: The intricate pathophysiology of immune response following SARS-CoV-2 infection or vaccination - The antigenic presentation activates T helper cells, which in turn activate the B cells, which diversify into antibody producing effector B cells and memory B cells. Simultaneously, numerous additional infection-induced or vaccine-induced responses pertaining to the innate and adaptive immunity play significant role.

antigenic presentation following infection or vaccination activates T helper cells, which in turn activate the B cells. The latter diversify into antibody producing effector B cells and memory B cells. In addition, there are numerous additional infection-induced or vaccine-induced responses pertaining to the innate and adaptive immune system. The responses may protect against infection and further viral immune escape. Conversely, there are uncharacterized mutations outside of S that could facilitate SARS-CoV-2 immune evasion.

Genomic variations and phenomenal concerns

The SARS-CoV-2 genomic variants have been emerging and circulating around the world throughout the COVID-19 pandemic. Having evolved in certain geographical regions, they have spread to other regions. Some of them are Variants of Concern (VOC) and Variants of Interest (VOI) labelled by WHO [24]. In short, a VOC is a SARS-CoV-2 variant with demonstrable increase in transmissibility, increase in virulence or a significant change in clinical presentation, or decrease in effectiveness of public health measures or available diagnostics, vaccines, therapeutics. Whereas a VOI is a SARS-CoV-2 variant with genomic changes affecting transmissibility, disease severity, immune escape, diagnostic or therapeutic escape, and ability to enhance community transmission resulting in multiple COVID-19 clusters at multiple geographical locations with increasing number of cases or having other epidemiological impacts to leading to an emerging risk to global public health.

Presently, VOCs include Alpha (B.1.1.7 – UK), Alpha^[K] (B.1.1.7 with E484K), Beta (B.1.351 – SA), Gamma (P.1 – Brazil), and Delta (B.1.617.2 – India). In addition, there are VOIs, which include Epsilon (B.1.427/B.1.429 – US), Zeta (P.2 – Brazil), Eta (B.1.525 – multiple countries), Theta (P.3 – Philippines), Iota (B.1.526), and Kappa (B.1.617.1 – India). The lists are likely to be larger in near future. Simultaneously, more infectious variants will keep on replacing those less infectious throughout the world regions and population groups. The WHO has declared Epsilon (1 March 2021 – California, the US), Zeta (17 March 2021 – Brazil), Eta (17 March 2021 – originated in Nigeria, now in multiple countries), Theta (24 March 2021 – Philippines), Iota (24 March 2021 – New York, the US), and Kappa (4 April 2021 – India) as VOIs. Another variant, A.23.1 with altered spike, has emerged and is responsible for Uganda epidemic [25].

It is likely that the VOIs and VOCs are the result of selective pressures and adaptation of the virus during periods of prolonged infections and subsequent transmission. Further, there is a convergent association of mutations as well. Potentially, such variants containing new mutations will continue to emerge in different geographic locations as the result of intra-host selection and subsequent transmission. The SARS-CoV-2 VOCs and VOIs cause a significant increase in transmissibility or virulence or both. Further, it has been speculated that SARS-CoV-2 may continue to accumulate mutations that evade immune responses. The major SARS-CoV-2 Variants have been classified by the Centers for Disease Control and Prevention (CDC) into 3 broad categories, VOIs - Variants of Interest, VOCs - Variants of Concern, and VHCs - Variants of High Consequence [26]. The classification relates the etiopathological correlates to the infectivity and virulence of the emerging variants (Figure 4).

PANGO Lineage	WHO Label	First outbreak and date	Notable mutations
Variants of Interest (VOIs) Epsilon, Zeta, Eta, Theta, Iota, and Kappa			
B.1.427/B.1.429	Epsilon (ε)	United States	S13I, W152C, L452R
P.2	Zeta (ζ)	Brazil	E484K, V1176F, F565L
B.1.525	Eta (η)	Multiple countries	E484K, F888L, ΔH69/ΔV70
P.3	Theta (θ)	Philippines	E1092K, H1101Y, V1176F
B.1.526	Iota (ι)	United States	D253G, E484K, L452R
B.1.617.1	Kappa (κ)	India	P681R, E484Q, L452R
Variants of Concern (VOCs)			
B.1.1.7	Alpha	United Kingdom	69–70del, N501Y, P681H
B.1.351	Beta	South Africa	K417N, E484K, N501Y
P.1	Gamma	Brazil	K417T, E484K, N501Y
B.1.1.7 with E484K	Alpha ^[K]	United Kingdom	69–70del, E484K, N501Y, P681H
B.1.617.2	Delta	India	L452R, T478K, P681R
B.1.617.2.1 or AY.1	Delta Plus	Multiple countries	L452R, T478K, P681R, K417N
Variants of High Consequence (VHC)			
None identified or labelled so far			

Figure 4: The Variants of Concern (VOCs) and Variants of Interest (VOIs), the WHO nomenclature, geographical evolution, and notable mutations.

The B.1.1.7, also called 501Y.V1 variant, emerged in the UK, during September 2020. It is significantly more infectious and has 18 mutations including 9 in the S gene and others in ORF1ab / ORF8/ N. It has N501Y mutation in S affecting bonding to the human ACE2 receptor and being considered more virulent than D614G, able to cause severe disease in a higher proportion of patients. The current vaccines appear to fully protect against B.1.1.7 variant.

The B.1.351, which originally emerged in South Africa, has 8 mutations, 5 in S including the N501Y mutation found in the B.1.1.7 variant, and others in ORF1ab / E / N. The B.1.351 (501Y.V2) variant carries additional immune evasion mutations, notably the E484K (Glu484→Lys) mutation and appears to not well-recognized by the immune systems of people previously infected with D614G. The variant shows substantial reduced neutralizing activity of therapeutic monoclonal antibodies (mAbs). Further, the vaccine efficacy is not strong to this variant.

The Gamma variant, P.1 carries 21 mutations including 10 in S including N501Y, others are in ORF1ab /ORF3a /ORF 8 /ORF9 /ORF 14 /N. In short, it incorporates E484K on the B.1.1.7 background. Given that the N501Y (Asn501→Tyr) mutation arose spontaneously in Alpha, Beta, and Gamma variants, it appears to confer a competitive advantage for the SARS-CoV-2 variants by increasing the affinity of spike for ACE2 and together with other less well characterized mutations has resulted in enhanced infectivity.

The Delta (B.1.617.2) genome has 13 mutations, 15 or 17 according to some other sources. The three of them, L452R, T478K, P681R, present the spike protein are of particular concern. The Delta Plus variant is supposed to be formed due to a mutation called K417N in the Delta or B.1.617.2 variant. There is exchange at position 417 (lysine-to-asparagine substitution) in Delta plus variant. The K417N mutation in S protein is associated with immune escape and reduced susceptibility to vaccine, and mAbs therapy. Globally, more than 12 countries have detected Delta Plus cases.

Basics of immunity and immune system failure

Imperfect humoral, t-cell, and interferon response

The infection with seasonal and cross-reacting CoVs is common in humans. In general, the CoVs do not provoke a fully protective immunity, and repeat infections are common. The studies show that detectable antibody levels wane over the first few months, post-infection [27]. This is exemplified by the ineffective serum antibody levels against the seasonal human coronavirus OC43 - HCoV-OC43 [28]. Similarly, the vaccines tend to be non-efficient at preventing seasonal CoV infection [29]. But the HCoV-specific immunity may wane but is not lost. In fact, they are less efficient than natural infections at provoking immunity and carry risks of adverse cross-reactions. As related to the SARS-CoV-1 infection, the humoral immunity may last up to 2 to 3 years, but antigen-specific T cells against the virus have been detected 11 years after infection [30].

The nature of the immune response after natural SARS-CoV-2 infection is complex and diverse. There are intricacies in COVID-19 dynamics and immunological characterization to SARS-CoV-2 infections. There is evidence of pre-existing T cells and antibodies capable of cross-reacting with SARS-CoV-2 suggests that immunological memory responses elicited during infection with seasonal coronaviruses may also affect COVID-19 susceptibility and disease risk as well as clinical manifestations. In this context, it has been hypothesized that severe COVID-19 manifestations may arise due to presence of non-neutralizing antibodies from prior CoV infections [31]. Further, the T cell-mediated response is likely to play an important role in regulating the SARS-CoV-2 viral replication and disease manifestations.

There are variations in the immune response to a primary SARS-CoV-2 infection. The individual factors like earlier exposure to a CoV infection as well as the genetic factors may lead to different immune landscapes and affect clinical manifestations and severity of the disease. Considering the common four circulating HCoVs in children and adults which cause common cold and that the primary infections usually occurs early in life, the reinfection with a CoV later may cause a recall response. The pre-existing non-neutralizing antibodies from prior CoV infections as well as the T-cell-mediated response dependent on tenacity and recall of immune memory in a population group, thus, may affect the course of the pandemic ranging from recurring outbreaks and resurgence to its near-elimination.

Loss of neutralizing epitopes in the S protein in the SARS-CoV-2 variants is likely to reduce the immune response [32]. In this context, the T cell mediated response may feature as a superior correlate of protection (CoP) against COVID-19 as the new more infectious and virulent variants emerge. The CD4+ and CD8+ T cell response encompasses specificity to several hundred epitopes across the entire SARS-CoV-2 proteome, the majority of which are unpaired in the virus.

The T cell epitopes that are altered in the SARS-CoV-2 variants are likely to bind to the various human leukocyte antigen (HLA) molecules presenting antigenic peptides to T cells, even when binding affinities are altered. Thus, the variants, such as Alpha variant, disabling the first line of immune defense, get more time to multiply, and may overcome the T cell mediated response.

There exists another line of anti-viral defence, represented by production and secretion of interferon by the host cells. But like many other viruses, SARS-CoV-2 has evolved mechanisms to reduce its exposure to IFN-I [33]. Its Alpha variant drives down the production of interferon by infected lung cells by flooding with Orf9b proteins. Whereas the Beta and Delta variants drive down interferon production in the infected cells through a different mechanism. The nsp13, nsp14, nsp15, and orf6, orf8, and the M protein are potent inhibitors of the MAVS pathway, leading to inhibition of IFN β production. The severe COVID-19 is associated with exhaustion of CD4+ and CD8+ T cells, as a result of deficient IFN-I production. Further, the IFN-I production, is significantly impaired in obesity and metabolic syndrome, and with ageing.

The erratic and overactive immune reactions

The innate immunity is the first line of defence against the SARS-CoV-2 virus invasion. The recognition of pathogen results in subsequent cytolytic immune responses, mainly through the type I interferons (IFN) and natural killer cells. The adaptive immunity also plays an important part in viral clearance via activated cytotoxic T cells that destroy virus-infected cells and the antibody-producing B cells target virus-specific antigens. The anti-viral immune response is crucial to eliminate the invading virus, but an overactive and persistent anti-viral immune response may lead to massive production of inflammatory cytokines and damage the host tissues. One of the major causes of ARDS in COVID-19 patients is a hyperactive immune system. The overproduction of cytokines caused by aberrant immune activation is known as a cytokine storm. The alveolar macrophages expressing ACE2 are a prime target cells for SARS-CoV-2 infection and these activated macrophages may play an important role in the hyperinflammatory syndrome due an overactive Immune response [34].

There is a complex immune landscape generated by SARS-CoV-2 infection [35]. The issue of immunity with SARS-CoV-2 infection is complex and COVID-19 as a disease weakens the immune system as well as leads it to act in erratic manner leading to the cytokine storm in certain cases. The immune efficacy with respect to susceptibility does not appear to prevent reinfection, but may attenuate the severity, possibly retard reinfection and may or may not reduce transmissibility or infectiousness. There is possibility that symptoms due to a CoV reinfection may be mild, and the virus may be cleared more quickly. The rapid rise in both IgM and IgG following a CoV infection, indicates that earlier primary infection with a common endemic HCoV strain provokes a recall response and the resurged HCoV-specific immunity may influence the course of COVID-19 illness.

The viral variant and other pathogen characteristics also have impact on the course of COVID-19 infection and disease. Patients with severe disease have substantially lower lymphocyte counts with reduced number of CD4+ T cells, CD8+ T cells, and natural killer cells. Whereas the proinflammatory subsets of T cells, including IL-17-producing CCR4+ CCR6+ CD4+ (T-helper 17 or Th17) cells and perforin and granulysin-expressing cytotoxic T cells are increased. It has been indicated that the particular helper T cell population, tissue-resident memory-like Th17 cells (Trm17), in the lungs of patients with severe COVID-19 may be central to the development of hyperinflammation, lung injury, and subsequent ARDS. In addition, there are present high plasma concentrations of inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF). The Trm17 cells may become activated as part of a cytokine storm, during which they start producing inflammatory molecules like GM-CSF [36].

Various clinical reports suggest that a subgroup of severely affected patients exhibit a hyper-inflammatory response to COVID-19 (COV-HI). The cytokine storm is associated with COV-HI and organ damage in severe COVID-19. The exaggerated production of inflammatory cytokines including TNF- α and IFN- γ leads to inflammatory cell death and PANoptosis, characterized by gasdermin-mediated pyroptosis, caspase-8-mediated apoptosis, and MLKL-mediated necroptosis [37]. This group of patients has a higher plasma concentration of IL-2, IL-7, IL-10, granulocyte-colony stimulating factor, IFN γ -induced protein-10 (IP-10), macrophage chemoattractant protein-1, macrophage inflammatory protein 1 α , and TNF. There may be hypercytokinaemia, unremitting fever, cytopenias, hyperferritinemia, and multi-organ damage, in these severely ill patients.

Immune response to COVID-19 vaccines

The present vaccines available for COVID-19 prophylaxis are based on the wild-type viral S protein. Most vaccinated

people develop neutralizing antibody (Ab) with an IC50 (half maximal inhibitory concentration) within the protective margin, although precise correlates of protection (CoP) are unknown. Variants with E484K mutations and other escape mutants may bring down vaccine efficacy, prompting the need for new and updated vaccines [38]. Further, there is a complex immune landscape generated by vaccination program in face of prevalence of various SARS-CoV-2 variants as the population groups may comprise of non-exposed, exposed, and non-infected, and exposed and infected persons with history of asymptomatic or mild disease and those with moderate to severe disease. Further, the individual immune response and the cumulative immune landscape of the population are important for SARS-CoV-2 primary and secondary infection and vaccination and determine the prospect for the pandemic.

As the pandemic is evolving and spreading to newer geographical regions, various genetic, racial, geographical, and socioeconomical factors are bound to influence the course of the pandemic. Various analyses consider that the severity of infection with SARS-CoV-2 may change in due course over a span of years in future. The epidemiological and immunological data indicate that the infection-blocking immunity for the virus wanes rapidly, but that disease-reducing immunity is long-lived [39]. Further, there is likely to be transition from epidemic to endemic dynamics associated with a shift in the age distribution of primary infections to younger age groups. Here, an optimistic model envisages that once the endemic phase is reached and primary exposure is in childhood, the virulence of SARS-CoV-2 may go down. Further, depending on its immune response, a vaccine could accelerate the state of mild disease endemicity by cultivating herd immunity. However, there might be a different outcome for the emergent infection causing a severe disease in children. Both situations reinforce the importance of vaccination and behavioral practices for disease containment.

There is question of the functional immunity to reinfection, disease, and carrier state with viral shedding and the endemicity of SARS-CoV-2 in the long run. The longitudinal analysis of SARS patients provides an opportunity to measure the durability of immune memory in the absence of re-exposure. In contrast to the antibodies, the memory T cells persist for much longer periods in animal models, and the immunity induced by previous strains is potent to prevent severe disease. However, the effect of genomic variation may influence the vaccine-induced immunity in light of the narrow epitope repertoire of currently available vaccines. On the other hand, the immune evasion is supposed to come at a biological fitness cost to the virus and impose an upper limit to the number of probable mutations when faced with the neutralizing antibody repertoire [40]. The similar mutations arising recurrently in the spike through convergent evolution in geographically distinct isolates also indicate that the spike variants offering a survival advantage to the virus are limited.

It appears that frequent and regular boosting of immunity by repeat doses of the COVID-19 vaccine may be required to maintain protection from the virus especially in light of temporary and waning immunity. Apparently, mimicking the natural immunity by vaccination may be a practical prophylactic strategy. Thus, during the transition of pandemic to endemicity, the SARS-CoV-2 infections may frequently occur in older individuals, and the immunity induced by infection or vaccination similar to that produced by natural infections in childhood may be a desirable outcome. Further, if the vaccine is able to cause a major reduction in transmission, in long run it may be suitable to consider strategies to vaccinate the older individuals for whom infection can cause a severe morbidity and higher mortality, while allowing natural immunity and transmission to be maintained in younger individuals.

Conclusion: current scenario and prospects

Unrestrained pandemic and future scenario

Using symptoms as a surveillance tool to curb the spread of SARS-CoV-2 is difficult, as milder reinfections increasingly contribute to ongoing transmissions [41]. Further, the infection or vaccination may protect against disease but may not provide transmission-blocking immunity needed for achieving significant long-term herd immunity. Furthermore, social distancing, masking, and an effective vaccination are critical for control of the pandemic and during its transition to endemicity. Once the endemic phase is reached and primary cases during childhood may manifest as mild disease, mass vaccination may no longer be necessary. But, if the primary infections in children are severe, then vaccination during childhood will need to be continued. Further, in light of the possible changes in the disease severity due to evolving variants and changing immunity landscape, we need to plan carefully for the transition to endemicity and the ongoing circulation of the virus.

Presently, the SARS-CoV-2 infection is so widespread with multiple evolving infectious variants that the hope of its elimination is bleak. However, there can be envisaged a possible outcome that the acquired immunity from infection,

reinfection and vaccination may lead to its endemicity [32]. As such, the future trajectory of the disease may be difficult to predict in a set of non-cohesive population comprising of various age groups, harbouring different risk factors, and having varied background in matter of exposure to the infection, manifestation of the disease, and inadequate immunization [42]. Further, though within-host emergence of escape mutants seems to be uncommon during early infection when viral loads are high, occurrence of immune-escape variants in high-viral-load samples emphasizes caution and need for continued vigilance [43].

The watchful and optimistic approach

The laboratory studies test the vaccine efficacy with a focus on level of the antibodies and their ability to block the virus from infecting cells, the immune response to the infecting virus is complex. In the human body the antibodies are a part of the immune response supplemented by the immune T cells, which help in curtailing the infection by identifying and eliminating the infected cells and help to protect from evolving a mild illness to severe disease [44]. Several COVID-19 vaccines appear to work against the VOCs and VOIs, as well. The earlier reports suggested that the vaccines might not work against of the variants, such as the Beta (B.1.351) variant, but the real-world data out of Qatar suggests that the Pfizer vaccine works satisfactorily well against it [45].

The immune response against the COVID-19 vaccine, in general, is robust. The full vaccination seems to offer 75% protection against B.1.351 infections, less than the 95% efficacy reported in the trials but still to a significant level. Simultaneously, there is evidence from clinical studies that the T-cell response may provide significant protection against emerging SARS-CoV-2 variants, as well [46]. There is evidence that when the vaccinated people get infected, are protected from the severe disease and serious outcomes [47]. Compared to this, the role of the vaccine in protecting Long Covid manifestations is being assumed, though not backed by large clinical studies [48].

Upgradation of the COVID-19 vaccines

On entering host cells, the SARS-CoV-2 virus starts replicating. With replication, the chances of random errors, or mutations, crop up during the viral replication cycle, despite the proofreading function of the nsp14 protein. Most of these errors are inconsequential, only a few being of epidemiological concern. Various mutations or their particular combinations, which improve the survival SARS-CoV-2 virus are emerging in different world regions, a phenomenon known as convergent evolution [49]. These particular combinations of mutations are seen to occur over and over again. The first major variant with spike-protein mutation, D614G has helped transmission of SARS-CoV-2 world over. Later, the Alpha (B.1.1.7) variant, has fast replaced those less infectious. The mutation, E484K helps the virus to evade the immune response. In due course, the variants carrying advantageous mutations outcompete a variant that is lacking them and replace it [50].

In fact, the phenomenon of convergent evolution may be a hopeful sign, as the virus may run out of ways to adapt to its habitat. In fact, the convergent evolution may be seen as the game of Tetris, where a limited number of building blocks can be assembled in different but limited combinations [51]. Thus, controlling infections, may hopefully limit the number of evolving variants, and vice versa. There is another aspect of phenomenon of convergent evolution. Faced with new variants, the current vaccines will eventually but gradually become less effective. But, as the virus has a limited number of viable mutations, the vaccines may be updated time to time based on the immunodynamics of evolving SARS-CoV-2 variants to maintain their efficacy. Further, the variant-specific boosters will prompt a more effective immune response against the new variants. Further, mixing vaccines could help boost immunity and help stop variants from bypassing the immune system. The odds are that the newer variants will continue to evolve, hence we have to update and revise our tools and tactics.

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Chapter 2: Pulmonary Involvement in COVID-19 and ‘Long Covid’: The Morbidity, Complications and Sequelae

Background

Introduction - the perennial pandemic: There are serious challenges posed by the SARS-CoV-2 virus and COVID-19 as the disease. With the persistence of the pandemic over one and half year, it is being feared that the Covid-19 may have become the new reality associated with human existence world over and the mankind may have to live with it for years or even decades. Further, the grievous nature of the disease is evolving further with genomic changes in the virus in form of mutations and evolution of variants, with enhanced infectivity and probably virulence.

Acute and chronic phases of COVID-19: Epidemiologically, it is becoming clear that apart from the advanced age and pre-existing conditions, such as diabetes, cardiovascular, pulmonary, and renal diseases, certain constituent factors render some patients more vulnerable to more severe forms of the disease. These factors influence the COVID-19 manifestations, its course, and later the convalescence period as well as the newly defined ‘Long Covid’ phase. The substantial continuing morbidity after resolution of the infection indicates persisting multisystem effects of ‘Long Covid’.

Lung damage associated with COVID-19: COVID-19 is primarily a respiratory disease presenting with a broad spectrum of respiratory tract involvement ranging from mild upper airway affliction to progressive life-threatening viral pneumonia and respiratory failure. It affects the respiratory system in various ways across the spectrum of disease severity, depending on age, immune status, and comorbidities. The symptoms may be mild, such as cough, shortness of breath and fevers, to severe and critical disease, including respiratory failure, shock, cytokine crisis, and multi-organ failure.

Implications for the post-covid care: Depending on the severity of respiratory inflammation and damage, as well as associated comorbidities, duration of injury and genetics, the progressive fibrosis leads to constriction and compression of lung tissues and damage to pulmonary microvasculature. Consequently, the COVID-19 patients with moderate/severe symptoms are likely to have a significant degree of long-term reduction in lung function. Depending on the severity of the disease, extensive and long-lasting damage to the lungs can occur, which may persist after resolution of the infection.

Managing the Long Covid’s challenges: Given global scale of the pandemic, the healthcare needs for patients with sequelae of COVID-19, especially in those with lung affliction are bound to increase in the near future. The challenge can be tackled by harnessing the existing healthcare infrastructure, development of scalable healthcare models and integration across various disciplines with a combination of pharmacological and non-pharmacological modalities. Following clinical and investigational assessment, the therapeutic strategy should depend on the disease manifestations, extent of damage in lungs and other organs, and associated complications.

Introduction: the evolving pandemic

The SARS-CoV-2 virus and COVID-19

Following infection, the SARS-CoV-2 virus becomes an intracellular entity. The intracellular replication, ensuing cellular damage, and involvement of various cells in respiratory system, immune system, and other organs, propels the clinical course of the disease. While we continue to explore the agent factors, disease transmission dynamics, pathogenesis and clinical spectrum of the disease, and therapeutic modalities, the grievous nature of the disease is evolving further with the genomic changes in the virus and pathophysiological alterations and clinical manifestations of the disease. Further, it may not be possible to eradicate the intracellular virions, which may persist and continue to carry on the inflammatory process leading to the ongoing organ damage and manifestations of ‘Long Covid’.

The future course of the disease, of course, is said to depend on various known and unknown factors, many of them may not be modifiable. There are serious challenges posed by SARS-CoV-2 virus and COVID-19 as the disease that are further increased by mutations and evolution of variants with enhanced infectivity and probably virulence. The significance of viral mutations needs to be explored in this context, which may help in diagnostic workup, designing therapeutics to combat the disease and developing effective vaccines for its prophylaxis. In addition, the avenues for improving the immune response to the infection and following vaccine inoculation, and the immunity in general are to be explored and

harnessed. It is being increasingly realised that the COVID-19 may have become the new reality associated with human existence world over and the mankind may have to live with it for years or even decades [1].

Clinical spectrum of acute COVID-19 illness

COVID-19 is primarily a respiratory disease presenting with a broad spectrum of respiratory tract involvement ranging from mild upper airway affliction to progressive life-threatening viral pneumonia. Coming into contact with the mucous membranes lining nose, mouth, and occasionally eyes, the SARS-CoV-2 virus enters the host cells, multiplies intracellularly and the released virions infect other cells. As the virus attacks the cells, it travels down the airways, from upper to lower respiratory tracts, finally infecting the alveoli and manifesting as pneumonia. In general, a significant number of those infected with the SARS-CoV-2 virus are asymptomatic, and as documented in a recent systematic review, at least one-third of those infected remain asymptomatic [2]. The study included serologic surveys from more than 365,000 people in England and more than 61,000 in Spain. When analysed, a similar proportion of asymptomatic cases 32.4% in England and 33% in Spain was noted.

Thus, on being exposed to the SARS-CoV-2 virus, not all persons develop the disease. For those who develop the disease, there is a large variation in disease severity, which may partly be due to the genetic variability in the response to the virus [3]. The individual vulnerability to the infection, response following the SARS-CoV-2 exposure, and the clinical spectrum of COVID-19 are greatly variable. In general, older adults and people who have concurrent health conditions like heart disease, cancer, obesity, and diabetes are prone to develop serious manifestations. The clinical manifestations of COVID-19 illness have been grouped into Stages I to III, based on the need for hospitalization, need for oxygen supplementation, progression to respiratory failure, and other parameters of the disease severity (Figure 1). Presently, considering the delayed post-illness convalescence and persisting clinical manifestations, the resolution phase can be added to this, as Stage IV.

The COVID-19 affects the respiratory system, too, in various ways and degrees across the spectrum of disease severity, depending on age, immune status, and comorbidities. The patients with underlying lung disease such as asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease, etc. can suffer with worsening of respiratory conditions. The symptoms may be mild, such as fever, cough, and shortness of breath, to severe and critical disease, including respiratory failure, shock, and multi-organ failure (MOF). In general, most people who develop clinical COVID-19, manifest mild to moderate symptoms [4]. They may have a dry cough or sore throat, whereas a minority of them goes on to develop pneumonia, with ground-glass opacities on a chest CT scan. Further, about 14% of COVID-19 cases have severe infection affecting both lungs. On the serious side of the clinical spectrum, about 5% of all COVID-19 cases suffer with critical disease with extensive damage to the airways and the alveoli, developing into severe pneumonia or acute respiratory distress syndrome (ARDS). Further, about 20% - 30% of critically ill patients are shown to develop vasculopathy and clots in the lungs, heart, brain, and legs. There may occur disseminated intravascular coagulation (DIC).

The phases of SARS-CoV-2 lung infection

When the SARS-CoV-2 infection starts spreading into the respiratory tract and lungs, it triggers various symptoms and complications, and may be associated with constant coughing often without phlegm, and pain in chest. The pathophysiological processes underlying COVID-19 illness may or may not show clinical features of earlier or later phases.

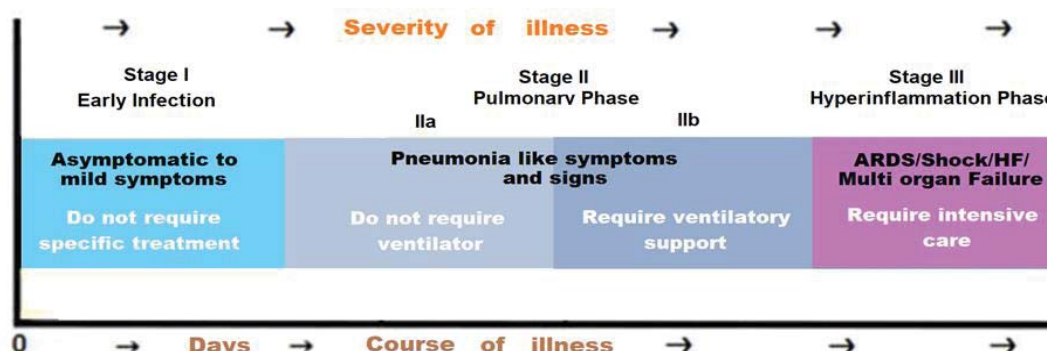


Table 1: The clinical spectrum of COVID-19.

Phase 1: Cell invasion and viral replication

The SARS-CoV-2 virus gains entry via ACE2 receptors, which are present on goblet (secretory) cells and on ciliated (hairy) cells in the nose, and through ACE2 receptors in the mucous cells of mouth and tongue.

Phase 2: Viral replication and immune response

As part of the defensive immune response, the lymphocytes begin to produce the IgM-type antibodies at first and later the longer-term specific neutralizing antibodies (the IgG type). In a German study, about 50% of the participants showed circulating IgM or IgG antibodies by day 7, and by day 14 all of them had developed antibodies [5]. Here, it is noteworthy that the antibodies titre may not predict the clinical course of the disease [6].

Phase 3: Lung inflammation and pneumonia

Approximately 13.8% of people with COVID-19 suffer with dyspnoea and severe disease and require hospitalization. Out of these, three-fourth patients may have evidence of bilateral pneumonia [7]. The pneumonia in COVID-19 manifests as consolidation and collapse of lung regions. There is reduced surfactant in the alveoli due to destruction of pneumocytes by the virus, infiltration by white blood cells, such as neutrophils and macrophages, as part of the immune response, and oedema due to injury to blood vessels and leakage in response to proinflammatory factors released by the inflammatory cells. The fluid accumulation compresses the alveoli from outside and in combination with lack of surfactant, leads to their collapse. As a result, the surface area in the lung for gaseous exchange is reduced leading to hypoxia and dyspnoea.

Phase 4: ARDS, the cytokine storm, and MOF

The critical illness in COVID-19, frequently develops in a period of about 10 days, though it can occur suddenly in a small proportion of those with mild or moderate disease. There occurs formation of fibrin clots in the alveoli and fibrin-platelet microthrombi in the small blood vessels in the lungs affecting gaseous exchange at the alveolar level. The cytokines, such as IL1, IL6, and TNF α damage and dilate the vessel walls, making them more permeable and may lead to cardiovascular shock. The angiotensin converting enzyme 1 (ACE1), in response to infection, leads to excess availability of angiotensin-2 from angiotensin-1, resulting in pulmonary vasoconstriction and leaky blood vessels.

The recovery or convalescence phase

The usual recovery time for mild COVID-19 is about two weeks and three to six weeks for severe disease. However, the recovery is variable and depends on Constitutional factors such as patient's age and pre-existing comorbidities in addition to the severity of the disease. The studies in the U.S. show that only 39% of those who had been hospitalized reported a return to baseline health by 14-21 days after diagnosis [8]. Similar findings have been reported from the European studies. In a study of 143 patients hospitalized for COVID-19, only 13% were symptom-free after a mean period of 60 days following disease onset [9]. The remaining 87% patients reported persistence of symptoms such as, fatigue, cough, dyspnoea, joint pains, and chest pain following discharge from the hospital, with over 55% patients continuing to experience three or more symptoms. As measured by the EuroQol visual analog scale, a decline in quality of life (QOL) as was noted in about 44% patients. The pneumonia-like manifestations may persist for several weeks in immunosuppressed patients. Even the patients with milder infection can suffer with have prolonged symptoms. A recent survey showed that about 65% of those infected returned to baseline health by 14-21 days after diagnosis [10]. The persisting symptoms with delayed recovery include cough (43%), fatigue (35%) and rarely fevers and chills in those with prior mild infection.

Pathophysiology of lung damage in COVID-19

SARS-CoV-2 infection: challenge to lung physiology

The alveoli are the basic functional units in lungs, where the oxygen from inspired air is exchanged with the carbon dioxide, which is expired subsequently. Normally, there is a tight connection between the alveolar type I (AT-I) cells and the capillaries. The AT I cells are thin and flat cells which line the alveolus, interspersed by alveolar type II (AT II). The type II pneumocytes secrete surfactant, which lines the walls of alveoli and prevents them from collapsing and sticking to each other at the end of a respiratory cycle, when the air pressure inside the lungs drops in the expiration phase.

COVID-19 infects alveolar cells (pneumocytes) leading to damage of the alveolar wall and the lining of the alveolus and capillaries. In addition, there occur microthrombi, which block the micro-vessels. The debris in form of plasma protein

accumulates on the alveolus wall and thickens the lining leading to the impaired gaseous exchange and oxygen transfer to the red blood cells. Simultaneously, there occurs loss of surfactant as the infection affects the surfactant producing cells, which are rich in ACE2 receptors [11]. Other contributory factors for loss of surfactant are environmental factors, like air pollutants and smoke, and a hyperactive immune response. The direct damage of the virus-infected cells as well as cytokine hyper-response reduces the availability of surfactant in the alveoli leading to their collapse at the expiratory phase, manifesting as considerable stress on respiratory muscles at subsequent inspiratory phase evidenced as dyspnoea and hypercapnia [12].

Inter-relationship of pathophysiology and clinical spectrum

The respiratory involvement in COVID-19 may be mild to moderate to severe (Figure 2). Depending on the extent of underlying pathophysiology in the mild disease there are infected AT I and II cells and presence of inflammatory cells and secretion of cytokines leading to reduced surfactant, vasodilatation, and reduced gaseous exchange leading to hypercapnia and hypoxia. Whereas, in a more severe disease, there occur increased interstitial fluid, widespread alveolar collapse, accumulation of protein and cellular debris and fibrosis leading to severely compromised gaseous exchange and inability to maintain tissue oxygenation in various organs.

To prevent redundant blood circulation through the collapsed alveoli, there occurs constriction of blood vessels supplying these alveoli. Depending on the severity of damage, the respiratory muscles work to handle the respiratory stress, but eventually tire, leaving the gaseous exchange compromised. In COVID-19, not only the respiratory cells richly endowed by ACE2 receptors are affected, the lung vasculature having ACE2 receptors is also infected and damaged impairing the compensatory blood redistribution from collapsed alveoli, resulting in significant redundant deoxygenated blood flow [13]. Further, the associated hypercoagulability with COVID-19, further hampers gaseous exchange in lungs and oxygen supply to various tissues and vital organs [14].

In addition, following infection, AT II cells release inflammatory signals to recruit immune cells including macrophages which release cytokines causing vasodilatation leading to increased permeability and fluid accumulation. The increased fluid dilutes surfactant and triggers alveolar collapse, leading to decreased gaseous exchange and increased work of breathing. The neutrophils recruited to the inflamed areas also release reactive oxygen species (ROS), which cause destruction of the infected AT I and AT II cells leading to widespread alveolar collapse precipitating ARDS. Finally, the protein rich fluid and debris enter the blood stream and precipitate systemic inflammatory response syndrome (SIRS), associated with septicaemia, shock, DIC, and MOF [15].

Host immune system and SARS-CoV2 infection

The viral genome typically consists of 6 open reading frames (ORFs), of which the ORF1a and ORF1b produce polypeptides, pp1a and pp1b, respectively, which in turn form non-structural proteins (NSPs). The remaining ORFs synthesise various structural proteins (SPs) including the spike and envelop proteins. The SPs induce immune response whereas NSPs appear to modify the host immune response. The SARS-CoV2 infection induces both innate and adaptive immune response and leads to infiltration by macrophages and T cells which release various pro-inflammatory cytokines/chemokines and lead to molecular changes in the lung tissue microenvironment.

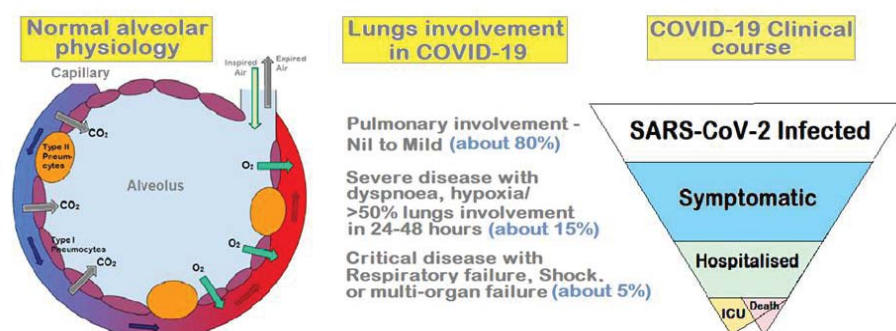


Figure 2: The alveolar morphology and physiology, pulmonary involvement, and the clinical manifestations.

The pro-inflammatory cytokines induce DNA damage, excessive production of angiogenic molecules (VEGF, IL-8, NO), ICAM-1 and VCAM-1, production of ROS and reactive nitrogen species (RNS), and alterations in cellular proteins and stimulation of cell proliferation and inhibition of apoptosis. The cytokines affect cells via activation of transcription factors like STATs, NF- κ B, and AP-1 by binding to their specific receptors and subsequent activation of intracellular kinases like Janus activated kinase (JAK), phosphatidylinositol-3-kinase (PI3K)/Akt, and MAP kinases. There can occur a sudden cytokine-burst, the cytokine release syndrome (CRS), leading to exacerbation of pneumonia and respiratory failure, and multiple organ dysfunctions. This is also associated with rapid progression of the viral infection, destruction of the immune system, and increased susceptibility to secondary infections.

There is another aspect of increased plasma level of TNF α , IL-6 and IL-1 β , which are present in COVID-19 patients. TNF α is a major associated pro-inflammatory cytokine, having a potential for DNA damage and cellular transformation through ROS in inflammation-associated carcinogenesis. The IL-6 promotes several pro-oncogenic pathways and genetic expression for cell cycle progression and regression of apoptosis, and suppression the host antitumor immune responses. Whereas other cytokines such as IL-1 α , IL-1 β , and IL-17, elevated in COVID-19 disease may affect the regulation of inflammation-related carcinogenesis. Further, IL-1 α has been related to increased cell proliferation and angiogenesis, and IL-1 β plays an important role in proliferation of epithelial cells in lungs. The COVID-19 patients, thus, have an increased propensity to develop cellular metaplasia. In this respect, the similarity and overlap in CT features between the COVID-19 illness and lung cancer progression has been highlighted and the widespread GGO findings in CT images of COVID-19 patients have raised the probability of developing lung cancer in due course. Thus, a follow up at regular interval is in Long Covid patients [16].

The long-term lung damage in COVID-19

As COVID-19 is a relatively new disease, the long-term effects of COVID-19 in those who recover, are still not known, but various recent observational case and cohort studies continue to provide data. Based on initial case studies from those with moderate-severe disease and those suffered with pneumonia, the initial damage to the lungs can persist leading to decreased lung function and impact the activities of daily living (ADL). Pulmonary fibrosis is one of the major complications of severe COVID-19 and even those fully recovered symptomatic patients, may have long-term lingering effects persisting for several months.

Depending on the severity of respiratory inflammation and damage, presence of comorbidities, duration of injury and certain ill-defined genetic factors, the chronic inflammation leads to epithelial damage and fibroblast activation, manifesting as pulmonary fibrosis. In due course, the progressive fibrosis may lead to constriction and compression of lung tissue and damage of pulmonary microvasculature. In addition, the lope-sided regeneration, the dysregulated fibroblastic activity and excessive deposition of hyaline, collagen, and other extracellular matrix proteins lead to alveolar damage and scarring in lungs. In case of about 23% of the recovered SARS patients, there was seen reduced lung exercise capacity and pulmonary function a year after infection [17]. The COVID-19 patients with moderate/severe symptoms are likely to have a similar level of long-term reduction in lung function. Thus, depending on the severity of the disease, extensive and long-lasting damage to the lungs can occur, continuing to persist after the recovery from the infection.

Autopsy findings in lungs of COVID-19 patients

A post-partum study involving 41 people died from COVID-19 in Italy has documented extensive damage, distortion of the pulmonary structure with scarring and massive blood clots in the arteries and veins [18]. Out of 41 cases, all 41 patients had extensive lung damage, while 36 of 41 (88%) had massive abnormal blood clotting in the lung arteries and veins. Further, in the study, nearly 90% of the lungs showed the fusion of smaller cells forming giant cells with several nuclei. The fused cells, or syncytia, are caused by SARS-CoV-2 S protein, which stimulates the fusion of infected cells with normal lung cells, leading to structural changes, inflammation, and abnormal blood clotting. The extent of damage to lungs in severe COVID-19 is, thus, enormous especially in those that are clinically vulnerable and suffer with a severe disease [19].

Autopsy findings reveal extensive lung damage, with firm, heavy and rubbery lungs with bilateral haemorrhagic edema, pleural effusion as well as signs of extensive shock characterized by variegated appearance of the liver and kidneys [20]. There is extensive endothelial injury associated with immune cell infiltration including T-lymphocytes and megakaryocytes. In the pulmonary vessels there is widespread thrombosis with microangiopathy and alveolar capillary microthrombi in addition to neovascularization and angiogenesis. The SARS-CoV-2 genome has been found

in respiratory cells, cells lining the blood vessels, and the syncytia, in these patients. These histopathologic changes are pathognomonic of COVID-19 pneumonia, and the persistence of the abnormal cells and the virus-infected cells may be linked with continuance of ongoing viral replication and organ damage, and persistence of Long Covid symptoms in those recovered from the disease.

The clinical correlates of lung involvement

Clinical presentation of COVID-19

Depending on the severity of damage, the respiratory involvement may appear as asymptomatic, mild to moderate respiratory illness, severe bronchopneumonia, or acute respiratory distress syndrome (ARDS).

Asymptomatic COVID-19 patients: A large proportion of healthy individuals, over 40%, though positive for SARS-CoV-2, do not exhibit clinically significant symptoms. They are, however, able to transmit the disease. The majority of these asymptomatic patients are from younger age group. But the asymptomatic patients not showing any signs of lung damage, may suffer subtle changes, potentially predisposing them for various long Covid-related complications in future.

In these asymptomatic COVID-19 patients, there have been shown lung abnormalities on chest CT scans. This is exemplified by the outbreak on Diamond Princess Cruise ship, at beginning of the COVID-19 pandemic in February 2020, where 73% of those positive were asymptomatic, of which 54% showed ground-glass opacities (GGOs) in lungs indicating alveolar edema, inflammation, and fibrosis in the lungs. In the retrospect, this could be an age-dependent effect and appears to occur to a lesser extent in younger patients.

Symptomatic COVID-19 patients: In most people, COVID-19 leads to very mild, mild, or moderate clinical manifestations. The variance in clinical presentation may be attributed to amount of viral load, age, pre-existing health conditions, genetic constitution, ethnicity/demographics, lifestyle, and environmental factors. It should be remembered that the majority of pathological and imaging data come from hospitalized COVID-19 patients rather than non-severe symptomatic patients who may not visit a medical facility for diagnostic workup or treatment [21].

Severe COVID-19 illness and pneumonias

The patients with severe disease manifesting as pneumonia and ARDS, exhibit extensive alveolar damage, capillary congestion, necrosis of AT I and II pneumocytes, and interstitial and alveolar edema. Simultaneously, there is AT II pneumocyte hyperplasia, squamous metaplasia with atypical cells and platelet-fibrin thrombi in small arterial vessels, and increased D-dimer levels. As these changes hinder the pulmonary function, and the higher the impairment, the higher is disease severity and mortality.

In severe disease, micro-thrombosis and associated ischemic events are common and the ARDS can occur due to the compromised gaseous exchange and the vascular insult to the alveolar architecture. The COVID-19 pneumonia presents with severe hypoxemia and altered respiratory mechanics [22]. The alveolar infiltration and the vascular insult are common factors responsible for the respiratory distress [23]. Accompanied with by hyper-activated coagulation cascade, with widespread micro- and macro-thromboses in the lung and in other organs and elevated serum D-dimer levels, the ARDS is associated with adverse outcomes. Simultaneously, the endothelial damage disrupts pulmonary vaso-regulation, promotes ventilation-perfusion mismatch, and promotes thrombogenesis. In the lungs, the ARDS directly impacts the alveoli and other tissues leading to extensive damage with scarring and fibrosis.

COVID-19 related ards and respiratory failure

With the progression of COVID-19 pneumonia, increasing number of alveoli become affected and filled with exudative fluid clinically manifesting as shortness of breath. Further progression leads to ARDS, a form of lung failure requiring respiratory support to improve gaseous exchange. The ARDS is a serious and potentially fatal complication, and in the survivors may have lasting symptoms due to pulmonary fibrosis and scarring. It is helpful to assess and categorize the COVID-19 patients as per symptoms and signs of the respiratory failure, as the ventilatory approach depends on the underlying pathology [24].

Broadly, the severe COVID-19 illness presents with two types of respiratory syndromes, the type 1 without ARDS, and type 2 with ARDS [25]. The two types may have overlapping characteristics. Further, during the early phases of

respiratory decompensation, the high transpulmonary pressures associated with spontaneous vigorous inspiratory effort may contribute to lung injury, called the patient self-induced lung injury [P-SILI] resulting in worsening of respiratory failure.

Type 1 or L Type: These patients present with near-normal pulmonary compliance with isolated viral pneumonia. The hypoxemia is associated with respiratory system compliance > 50 ml/cm H₂O and mainly due to the hypoxic pulmonary vasoconstriction and impaired regulation of pulmonary blood flow. There is, thus, severe hypoxemia due to ventilation/perfusion (VA/Q) mismatch and high PEEP and prone positioning may not improve oxygenation through recruitment of collapsed areas but redistribute pulmonary perfusion and improve the VA/Q relationship. In fact, long-term prone positioning/supine cycles is of little benefit in these patients. The PEEP levels should be kept lower in these patients with high pulmonary compliance. Respiratory rate should not exceed 20 breaths/min and doing too much should be avoided.

Type 2 or Type H: These patients present with decreased pulmonary compliance and severe hypoxemia is associated with compliance values < 40 ml/cmH₂O, indicating significant ARDS. The type 2 respiratory syndrome is seen in 20% – 30% of COVID-19 patients admitted to the ICU. The patients may transit to a clinical picture characteristic of ARDS, with extensive CT consolidations, high elastance (low compliance), and higher lung weight as assessed by CT scans. These patients respond to high PEEP by increasing aerated lung size by recruiting previously collapsed lung units. But the high transpulmonary pressure may not be well-tolerated by some patients. A relatively low tidal volumes, coupled with modest hypercapnia, facilitate the goal of minimizing ventilator-induced lung injury (VILI) and prone positions are helpful.

Following onset of respiratory distress, patients initially retain relatively good compliance despite compromised oxygenation, may not appear overtly dyspnoeic, and are termed type L. The infiltrates at this stage are limited in extent and characterized by a ground-glass pattern signifying interstitial edema, and lower lung weight as assessed by CT scans. There are chances that the clinical condition may stabilize at this stage without further deterioration. But, if pneumonia and lung edema increase in these patients, either because of the disease inciting inflammation and/ or P-SILI, the type H phenotype may progressively develop. Over time, the unchecked viral disease promotes inflammation and local as well as generalized thrombogenesis, intense cytokine release, right ventricular overload, and systemic multi-organ dysfunctions. In the advanced state, it is advisable to apply a conventional lung-protective strategy: higher PEEP (≤ 15 cm H₂O), lower tidal volume (6 mL/kg), and prone positioning while minimizing oxygen consumption. A daily check of coagulation parameters, in particular D-dimer levels, in both the type 1 and the type 2 patients and judicious anticoagulation is helpful [22].

CT imaging in COVID-19 and post-covid follow up

CT imaging during acute COVID-19 illness

The computed tomography (CT) is an important tool for early diagnosis and monitoring of the affliction of lungs in COVID-19. The GGOs, dense opacities obscuring underlying vessels and bronchial walls, are common in COVID-19. Studies have shown a higher frequency of multifocal, bilateral, peripheral, and nonspecific distribution of GGOs with sub-segmental patchy consolidations in SARS-CoV2-infected individuals compared to controls [26]. Another study highlighted that more than 50% of the SARS-CoV2-infected patients have significant ground-glass and consolidative opacities on chest CT scans [27]. The chest CT scans can be helpful for the diagnosis as well as for monitoring the prognosis.

There are peripheral lung GGOs seen in CT imaging of the chest. Peripheral pulmonary vascular changes are less well characterized. The effects of SARS-CoV-2 infection on the alveolar architecture manifesting as GGOs depend on the severity of the infection and its effects on the immune system, and imply partial collapse of alveoli, partial filling of air space, and interstitial thickening. The severity of the disease is related to the extent of lesions on initial chest CT scans and the abnormalities on later CT scans have been related to the disease course [28]. In general, during the course of the disease, the GGO occurs from the beginning of COVID-19 and tends to decrease after 14 days, whereas consolidations appear around day 9, followed by fibrosis after 14 days.

There are typical, indeterminate, and atypical findings on CT Imaging in COVID-19 (Figure 3). The typical findings are bilateral GGOs with areas of consolidation, associated with septal thickening. The scans may show multifocal round GGOs with areas of consolidation or the GGO areas surrounded by complete and incomplete rings of consolidation. The indeterminate findings are bilateral diffused GGOs associated with consolidations with some areas of septal thickening

CT Scan Findings in Lungs in COVID-19	
Typical findings	<ul style="list-style-type: none"> - Bilateral GGOs with areas of consolidation associated with septal thickening - Multifocal round GGOs with areas of consolidation - GGO areas surrounded by complete and incomplete rings of consolidation
Intermediate findings	<ul style="list-style-type: none"> - Bilateral diffused GGOs associated with consolidations with areas of septal thickening - Unilateral GGOs in a lung segment - A small GGO with a non-rounded and non-peripheral distribution
Atypical findings	<ul style="list-style-type: none"> - Isolated segmental consolidation - Discrete small centrilobular nodules - Pulmonary cavitations - Bilateral smooth interlobular septal thickening with pleural effusion

Figure 3: The typical, indeterminate, and atypical findings on CT Imaging in COVID-19.

or unilateral GGOs in a lung segment or a small GGO with a non-rounded and non-peripheral distribution. Whereas, the atypical findings are isolated segmental consolidation, discrete small centrilobular nodules, lung cavitations and bilateral smooth interlobular septal thickening with pleural effusion [29]. In general, at time of initial presentation 88% patients show GGOs with bilateral involvement, 80 % show posterior distribution, 79% have multi-lobar involvement, and 76% have peripheral distribution, whereas only 32% display consolidation on initial presentation [30].

The pulmonary fibrosis is a major consequence of SARS-CoV-2 infection and primarily results due to direct alveolar damage and as the fallout of ARDS. The effects of pulmonary fibrosis and ongoing damage in the lung are also observed later in the absence of the infection and have been attributed to the persistent hyper-inflammatory state, with the elderly being at higher risk. Further, SARS-CoV2 is a cytopathic virus that can induce host cell lysis following infection. The virus led pyroptosis causes apoptosis along with excessive immunologic response, resulting in increased IL-1 β level and cytokine storm. The CT findings of GGOs have also been correlated with increased expression of ACE2. There take place different stages of pulmonary tissue damage in the lungs of COVID-19 patients with the appearance of GGOs, and include consolidation, reticular pattern, crazy paving pattern, air bronchogram including the airway changes, pleural changes, sub-pleural curvilinear line, and finally, fibrosis and scarring seen on CT images.

CT imaging for the long-term follow up

A long-term study highlighted that in the SARS infection, the fibrosis-like findings on CT in recovering patients diminish over time [31]. It is expected that similar prognosis may be possible in convalescent COVID-19 patients [32]. In the Post-COVID-19 patients, the follow up CT scans may reveal probable lifetime lung damage in about one-third of the patients. About 20% - 30% of patients who have suffered mild disease may have persisting diminished lung function and exercise capacity, whereas in 55% of patients with critical disease may continue to have the lung function impairment three months following hospital discharge. Further, there has been shown a definite correlation between initial chest CT scan involvement and impaired PFT [33].

The lung function, exercise capacity, persistent radiologic abnormalities, and quality of life data have been related to radiologic lung involvement at admission. In fact, the later radiological and functional sequelae have been related to initial lung involvement on CT scans. On chest CT, the main abnormalities are GGOs at hospital admission and fibrosis 3 months later, and the patients may remain disabled 3 months after discharge in terms of lung function, exercise capacity, and QoL. The radiologic impairment may improve following recovery, but normalization is seen only in a small number of patients. In general, about 12%-23% COVID-19 hospitalized patients show restrictive pattern on PFT one month after discharge [33]. In the study, the exercise capacity was still poor 3 months after ICU discharge and decreased QoL was associated with severity parameters during ICU admission and chest CT abnormalities on admission.

Pan, et al. analyzed 21 patients (6 men and 15 women aged 25–63 years) with confirmed COVID-19 with a total of 82 chest CT scans and reported that in patients recovering from COVID-19 without severe respiratory distress during the

clinical course, lung abnormalities on chest CT scans showed greatest severity approximately 10 days after initial onset of symptoms [34]. The follow up CT studies revealed that the lung damage may persist in post-COVID-19 patients and over one-third of recovered patients follow-up CT scans after six-month show pulmonary fibrosis [35]. In a follow-up CT scans study involving 114 patients who recovered from severe COVID-19 pneumonia, about 62 percent still showed evidence of abnormalities on the scans after 6 months, whereas about 35 percent had fibrosis-like features indicating potentially permanent damage, such as honeycombing patterns and parenchymal bands. In all, about up to 63% of those suffered with ARDS had lingering lung involvement [35].

COVID-19 follow up: links with neoplastic lesions

The SARS-CoV-2 Infection causes molecular changes and recruitment of inflammatory cytokines/chemokines in lung tissue microenvironment [16]. As well known, several pro-inflammatory cytokines are involved inflammation-associated neoplastic alterations through various molecular and metabolic pathways, and ROS. The widespread GGO findings in CT images of COVID-19 patients have raised the probability of developing lung cancer and highlighted need for a regular follow up for early detection of any pre-neoplastic lesions.

The disease continuum from COVID-19 to Long Covid

Factors influencing the pulmonary manifestations during disease course

It is becoming clear that apart from the advanced age and pre-existing conditions, such as diabetes, cardiovascular, pulmonary, and renal diseases, certain constituent factors render some patients more vulnerable to the more severe forms of the disease including pneumonia and ARDS. In addition, certain still unknown factors may influence the clinical manifestations, its course, and later the convalescent phase. From the clinical perspective, knowledge of the host constituent factors, including the genetic variations, may improve provision of healthcare for patients with COVID-19 during the acute phase of the disease as well as during the convalescence and 'Long Covid' phase. The host genetic factors have been linked to the variable clinical manifestations of the disease following exposure to the virus at the individual level as well as in various population groups [36]. In fact, a model to understand several related factors such as age, associated co-morbidities and genetic factors including human genomic variants linked to COVID-19 outcomes can be conceived as a continuum of the clinical course of the disease and later period (Figure 4).

The genetic factors and pathways related to the disease manifestations involve specific deviations in the genes and pathways responsible for inter-individual COVID-19 susceptibility and response. To track the acute as well as long-term impact of the disease on health, the project called the 'COVID Human Genetic Effort' aims to find genetic variants that compromise the immune systems and render certain individuals more vulnerable to the risk of developing COVID-19 [37]. In addition, the project aims to document the genetic variations which make some individuals resistant to the SARS-CoV2 infection. In nutshell, the project aims to discover, monogenic inborn errors of immunity (IEI) underlying severe forms of COVID-19 in previously healthy individuals, monogenic variations which make certain individuals resistant to the SARS-CoV2 infection despite repeated exposure, and decipher the molecular, cellular, and immunological mechanisms by which they cause resistance to the viral infection or predisposition to a severe form of the disease.

The COVID-19 delayed and long-term effects

There is a growing evidence of persisting multisystem effects of COVID-19, indicating substantial continuing morbidity

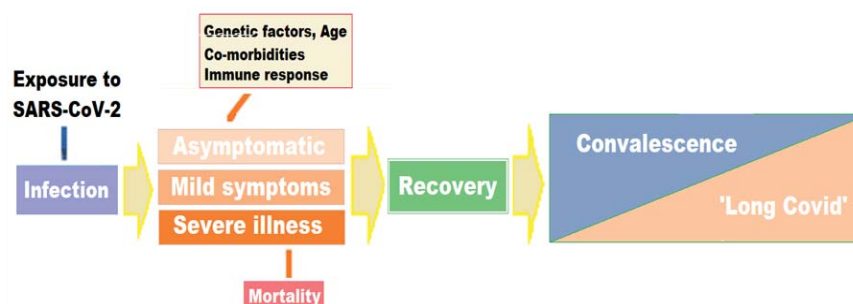


Figure 4: The factors related to the disease manifestations - clinical course, convalescence, and 'Long Covid'.

after resolution of the infection [9]. While most people recover quickly and completely from the virus, persistent manifestations, especially pertaining to respiratory system are frequently seen and the reports from various cohort studies suggest that one in three people may not fully recover several weeks after the initial illness and a smaller but still substantial proportion may continue to have symptoms and disabilities that persist for months [38]. Further, the long-term effects of COVID-19 are seen in the younger population also, though the risk of 'Long Covid' increases with age. People who suffer with severe form of the disease, experience long-term inflammation and damage in lungs, heart, immune system, brain, the vasculature, and other organs. These long-term effects may last for months and years. The 'Long Covid' is not contagious and results due to the body's response to the virus infection continuing beyond the initial illness.

Most COVID-19 patients recover within few weeks without significant complications. In others, often the persisting symptoms may go un-noticed, as they are vague and nonspecific. But some patients, even those who had mild versions of the disease, including the younger people afflicted with mild or asymptomatic disease and those who did not suffer with serious disease or require hospitalization, may continue to experience symptoms after their initial recovery [39]. These patients have been described as 'long haulers' and the clinical condition due to persisting or continuing symptoms has been called post-COVID-19 syndrome, 'Post-Acute Sequelae of SARS-CoV-2 infection (PASC)' or 'Long COVID-19', or 'Long Covid' in short. The clinical condition encompasses a delayed convalescence or recovery, persistence of symptoms, and emergence of symptoms related to the organs involved and damaged, and incapacitating complications and sequelae (Figure 5).

The long-haul COVID patients carry their symptoms well beyond the normal course of recovery lasting for weeks and months or longer. Further, of various facets of the disease, the Long Covid syndrome may in due course prove to be the most difficult to deal with. These symptoms are often varied and relatively common and may defy a COVID-19-related diagnosis. Several patients who are expected to recover, continue to suffer for a variable period of weeks and months with various general symptoms such as breathlessness on exertion, fatigue, dizziness, memory lapses and other cognitive issues, digestive disorders, erratic heart rates, headaches, fluctuating blood pressure, and muscular and joint pains, which are often considered by the patient himself and family members as related to the weakness developed following the disease. These patients report weeks- and months-long symptoms affecting lungs, heart and other organs and given the multitude of COVID-19 cases worldwide, the prevalence of 'Long Covid' is expected to be substantial and likely to increase with the recurrent outbreaks of the disease. Furthermore, the 'Long Covid' with debilitating and prolonged illness may have profound impact on health of people, their social life and livelihoods, and the economy.

The presentation of 'Long Covid' syndrome

The occurrence of persistence or appearance symptoms related to 'Long Covid' are being increasingly reported. Over the past few months evidence has mounted about the significant long-term effects of COVID-19 and millions of people are expected to be suffering with 'Long Covid' symptoms. The worldwide distribution of COVID-19 suggests that many of those people are currently living and experiencing the misery in the U.S., India, and various European countries. The 'Long Covid' is neither well-defined nor well understood, partly because the related research is still in its infancy. The symptoms persist or develop outside the initial viral infection, and the duration and exact pathogenesis are unknown. Further, they vary from vague to severe incapacitating symptoms, and there is often a relapsing and remitting pattern.

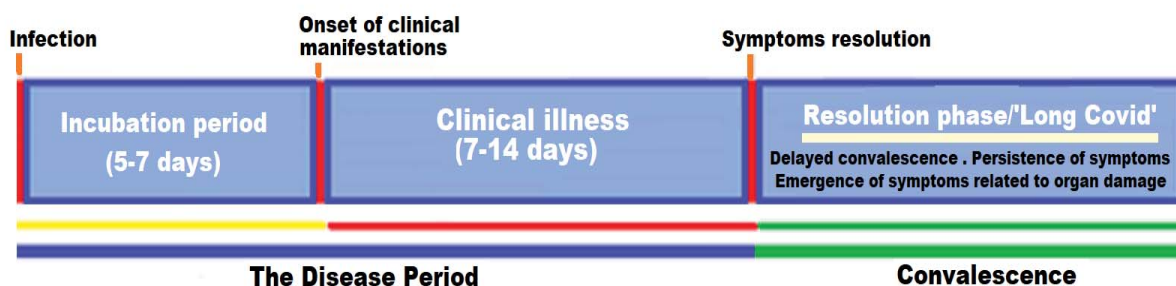


Figure 5: The abnormal convalescence or resolution phase following Covid-19 illness: delayed convalescence, persistence of symptoms, and emergence of symptoms related to organs affected, and prolonged recovery and incapacitating complications and sequelae.

There is little known about the prevalence, risk factors, or probability to chart the protracted course for 'Long Covid'. It appears that the etiology of the syndrome is multifactorial and may involve unbound immune responses, cardiopulmonary or systemic inflammation, vasculopathy and coagulation disorders, and a direct cellular damage from viral replication during the acute illness. The syndrome has vastly emerged from self-reporting but is a real clinical entity with chronic manifestations, and characterized by symptoms of fatigue, headache, dyspnoea, and anosmia and likely to increase with age, higher BMI, and female sex. Further, as deciphered from various studies, experiencing more than five symptoms during the first week of illness is associated with 'Long Covid' [40].

In a study with online survey data involving over 4,000 COVID-19 patients, about 13.3% of all ages suffered with the symptoms lasting over 28 days, whereas 10% of those aged 18-49 years had the related symptoms 4 weeks after acquiring the infection. Further, 4.5% patients of all age-groups suffered with the symptoms for more than 8 weeks, and 2.3% of all ages for more than 12 weeks. The study was conducted by health-science firm Zoe Global Limited in conjunction with Biomedical Research Centre based at GSTT NHS Foundation Trust and supported by the UK Research and Innovation [41]. The analysis and inference derived from similar studies could be used to identifying individuals with 'Long-Covid' may help to reduce long-term complications and sequelae and planning health education, guidance, and rehabilitation services [42].

Diagnosis and manifestations of 'Long Covid'

As a matter of fact, medical advice should be routinely sought for all the patients having delayed recovery and persistence or emergence of symptoms. There is a multitude of adverse physical and mental health effects due to 'Long Covid' and these afflictions may last for an indefinite period. According to a study published in the Lancet, which included 1,733 people tested positive for COVID-19 and followed for 4 months, documented that more than 75% of the people who were hospitalized for COVID-19, continued to suffer with at least one symptom for 6 months after recovery. Further, it was noted that about 76% of them experienced lingering symptoms of COVID-19 long after being cured of the illness [17].

In another recent study, Carvalho-Schneider et al. followed-up 150 adults with only mild to moderate COVID-19 illness for two-month and found that two thirds of them were still experiencing symptoms, most commonly shortness of breath, loss of smell and taste, and/or asthenia and fatigue [43]. Another study by Italian researchers, covering 143 COVID patients who had been discharged from the hospital, found that only about one in eight was completely free of symptoms 60 days from the beginnings of the illness [44]. The King's College London study, one of the largest surveys so far, reported that around 10% of patients had persistent symptoms for one month, with 1.5% to 2% having sustained symptoms at 3 months. Further, the study documented that 'Long Covid' was twice as common in women as men, and the older people, and those with more than five symptoms during their first week of illness were more likely to develop 'Long Covid' [41].

Management of 'Long Covid' syndrome

The clinical workup and general guidelines

There is envisaged a healthcare continuum for management of pulmonary manifestations of COVID-19 and 'Long Covid' (Figure 6).

It encompasses diagnostic workup, clinical follow up, investigational workup, followed by assessment of organ damage and treatment which involves pharmacological as well as non-pharmacological treatment in form of the holistic care.

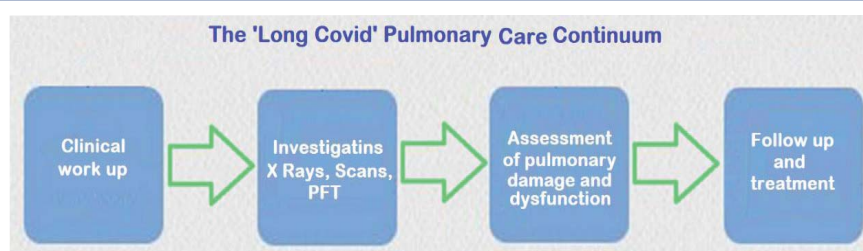


Figure 6: The 'long Covid' pulmonary care and management continuum – Diagnosis, Clinical follow up, Investigations, Assessment of pulmonary damage, and Supportive treatment.

General clinical guidelines

Chest pain: Non-specific chest pain is common in post-acute COVID-19. It could be musculoskeletal, unexplained non-specific chest pain, or due to a cardiovascular condition. Any persistent or recurrent pain in chest in setting of post-COVID-19 convalescence requires meticulous workup.

Respiratory symptoms: A degree of breathlessness is common during acute COVID-19 and convalescence. There could be worsening breathlessness and severe breathlessness may require hospitalization. In general, the breathlessness tends to improve with breathing exercises and guided pulmonary rehabilitation.

Thromboembolism: COVID-19 is an inflammatory and hypercoagulable state, with an increased risk of thromboembolic events including pulmonary thrombo-embolism. The hospitalized patients, in general, receive prophylactic anticoagulation followed by anticoagulant therapy after discharge in the high-risk patients for an extended period.

Other symptoms: Other symptoms such as anxiety, stress, and insomnia are common and may have a bearing on cardio-pulmonary status and care. The elderly patients, in addition, are more prone to risk of sarcopenia and malnutrition.

Investigations during 'Long Covid' follow up

Blood tests - Anaemia should be excluded. Lymphopenia is a feature of severe, acute COVID-19 illness, whereas leucocytosis may denote infection or inflammatory response.

The biomarkers - They include C reactive protein, d-Dimer, LDH, and ferritin indicative of inflammation and continuing prothrombotic state.

An ECG and Chest X-Ray - at 12 weeks or earlier for new, persistent, or progressive symptoms. Cardiac echo, CT scan chest or MR scan may be required.

Further studies and research are likely to refine the indications and interpretation of diagnostic and monitoring tests in follow-up of 'Long Covid'.

Supportive treatment and rehabilitation

The 'Long Covid' syndrome has multi-system involvement and unpredictable course with variable presentation depending on unmodifiable factors such as race, age and sex, and modifiable factors like comorbidities and lifestyle, and certain unknown factors. Following clinical and investigational assessment, the patients should be managed according to their clinical manifestations, extent of organ damage and associated complications. In case of suspected pulmonary and cardiac involvement, the restriction of physical activity advised, followed by periodic assessment. An early resumption of physical activity and exercise in the presence of pulmonary dysfunction may also be associated with both increased morbidity and mortality [45].

Although there are no firm data on COVID-19 recovery, many reports indicate that it may takes weeks until people with even moderate infections are back to baseline. If the pulmonary function evaluation is unremarkable and there are no further cardiopulmonary symptoms, the patient can slowly and gradually resume physical activity, beginning with short walks. Current recommendations for resuming physical activity following COVID-19 illness mention no exercise for 2 weeks from the positive test, close monitoring for symptoms, slow resumption of exercise for asymptomatic post-COVID-19 patients, those with Mild Post-COVID-19 symptoms are advised rest for 2 weeks, clinical evaluation, with consideration for X ray chest, ECG, and echocardiogram before resuming exercise. Whereas those having suffered with severe COVID-19 illness need to undergo complete cardiopulmonary evaluation during hospitalization and 2 weeks after discharge, close monitoring and supervised slow resumption of activity (46).

Activity guidance and occupational rehabilitation

In general, all COVID-19 patients should be risk stratified following recovery before recommending a return to physical activity, which should be gradual, individualized, and based on subjective tolerance of the activity (Figure 7). It is noteworthy that apart from the severe cases and elderly, even those with mild disease and a proportion of people from all age groups may experience a prolonged recovery [47]. In general, a return to physical activity should be after at least

S. N.	Activity phase	Activity details
1.	Phase One	Breathing exercises Mild stretching Gentle walking.
2.	Phase Two	Low intensity walking Mild household Gardening tasks Light yogic exercises
3.	Phase Three	Moderate intensity aerobic Moderate strength challenge
4.	Phase Four	Moderate intensity aerobic Strength challenge with coordination
5.	Phase Five	Return to regular exercise level, Regular physical activity pattern

Figure 7: The phases of physical activity and exercise.

seven days period free of symptoms, followed by two weeks of minimal exertion. As a rule, those with ongoing symptoms or history of severe COVID-19 need cardio-pulmonary assessment before advising return to physical activity [48]. In practice, thus, for those with mild symptoms during the COVID-19 illness and asymptomatic during convalescence period, there should be a phased return to physical activity with at least a week in between every phase.

The phases have been outlined as - Phase 1: Breathing exercises, mild stretching, and gentle walking; Phase 2: Low intensity walking, mild household and gardening tasks, light yoga; Phase 3: Moderate intensity aerobic and strength challenge; Phase 4: Moderate intensity aerobic and strength challenge with coordination and functioning skills; and Phase 5: Return to regular exercise and physical activity pattern. Usually, a light intensity activity is advised for initial two weeks. The Borg Rating of Perceived Exertion (RPE) scale is a subjective assessment of activity and physical work and helpful in guiding the progress through the phases of increasing physical activity. The patients must rate their subjective feeling of exertion, including shortness of breath and fatigue, on a scale from 6 (no exertion at all) to 20 - maximal exertion [49].

Conclusion: evolving 'Long Covid' scenario

Post-Covid-19 pulmonary damage and sequelae

The post-COVID-19 pulmonary damage and fibrosis is characterized by unsuccessful reconstruction of the damaged alveolar epithelium, persistence of fibroblasts and excessive deposition of collagen and other extracellular matrix components, and the destruction of normal pulmonary architecture. Its progression in due course results in compression and destruction of normal pulmonary parenchyma, and damage to microvasculature. There takes place fibrin deposition in the alveoli and lung parenchyma, together with platelet thrombotic micro-clots in the pulmonary vessels. The elderly patients are more prone to viral-induced fibrosis due to immunosenescence. The recent reports show that serum levels of the various cytokines and growth factors including monocyte-1 chemoattractant protein (MCP-1), transforming growth factor $\beta 1$ (TGF- $\beta 1$), tumor necrosis factor α (TNF- α), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), interleukin-1b (IL-1b) and interleukin-6 (IL-6), are overexpressed are also highly increased in COVID-19 patients. In addition, there occurs dysregulated release of matrix metalloproteinases, leading to epithelial and endothelial injury and uncontrolled fibroproliferation.

From the clinical perspective, the COVID-19 incubation period and clinical phase involves 3 weeks. In this context, the post-acute COVID-19 can be described as the illness extending beyond three weeks from the onset of first symptoms, and the chronic COVID-19 as extending beyond 12 weeks. As being increasingly documented, about 10% of patients who have tested positive for SARS-CoV-2 virus remain unwell beyond three weeks, and a smaller proportion for further period. In general, the diagnosis of the 'Long Covid' or 'Long haulers' should be entertained for various symptoms and signs linger well beyond the period of convalescence in COVID-19 [50]. The most common of persisting signs and symptoms of post-COVID-19 illness related to respiratory system include extreme tiredness (fatigue) and giddiness, chest pain and

COVID-19 associated pulmonary manifestations and fallouts

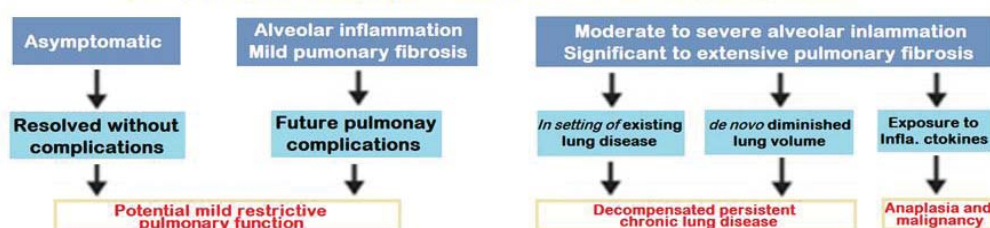


Table 8: Pulmonary manifestations associated with COVID-19 illness and their fallouts.

tightness, palpitations, shortness of breath and Cough. The underlying disease state may vary from mild restrictive lung function to decompensated persistent chronic lung disease (Figure 8).

The therapeutic options and innovations

Presently, there is no proven and fully documented effective therapeutic modalities for the treatment of post-inflammatory pulmonary fibrosis following COVID-19. But, as the disorder bears similarities in its pathogenesis with idiopathic pulmonary fibrosis including cytokine profiles, it has been suggested that the drugs useful in the treatment of Idiopathic pulmonary fibrosis (IPF) could also be beneficial for symptomatic and supportive therapy for post-COVID-19 patients.

Unquestionably, the most important factor in limiting pulmonary fibrosis is timely antiviral treatment and elimination of the causative agent. Though, currently, there is no fully substantiated therapeutic modality for the treatment of post-inflammatory pulmonary fibrosis after COVID-19, some therapies need to be considered [51]. The anti-viral agents can reduce the viral load and the duration of viral pneumonia, and hence prevent and decrease the pulmonary fibrosis. Thus, the currently known antiviral agents like remdesivir and favipiravir, especially when used early in the course of disease, may inhibit RNA replication due to high affinity to viral enzymes, reverse transcription or protein biosynthesis through premature termination or inhibition of nitrogenous bases synthesis. Remdesivir was found efficacious in inhibiting viral replication and restricting lung injury in the animal model of MERS infection. Favipiravir (FPV) may be another possible treatment option. It has been shown that FPV is able to inhibit virus reproduction *in vitro*. The preliminary studies indicate viraemic clearance and improved radiological appearance following favipiravir treatment.

The rationale for the use of steroids in COVID-19 viral pneumonia is to decrease the host inflammatory response in the lungs, which can lead to the development of acute lung injury and ARDS. The use of steroids in COVID-19 may also decrease the hyper-inflammatory activity in other organs. There are several reports to suggest that the use of spironolactone may be of significantly useful in fibrosis prevention. Tocilizumab, the monoclonal antibody against IL-6, has been claimed to have a beneficial effect on post-COVID-19 patients with severe lung damage and elevated interleukin six levels. As the final option, lung transplantation has been considered and tried [52,53].

The 'Long Covid' challenges and solutions

The SARS-CoV-2 virus uses ACE2 receptors to cause interstitial lung damage followed by parenchymal lesions. ARDS is the common acute pulmonary complication of the COVID-19, whereas pulmonary fibrosis is the sequelae of both acute as well as chronic ('long') COVID-19 leading to permanent disability. As mentioned earlier in this review article, there is no proven and fully documented effective therapeutic modalities for the treatment of post-inflammatory pulmonary fibrosis following COVID-19 illness.

Given the global scale of the pandemic both in the recent past as well as envisioned for the near future, the healthcare needs for patients with sequelae of COVID-19, especially in those with lung affliction are bound to increase alarmingly. Following clinical and investigational assessment, the therapeutic strategy is likely to depend on the clinical manifestations, extent of damage in lungs and other organs, and associated complications. The challenge can be tackled by harnessing of existing healthcare infrastructure, development of scalable healthcare models, novel research initiatives, and integration across disciplines with a combination of pharmacological and non-pharmacological modalities for improved physical and mental health outcomes for COVID-19 survivors in the long-run [54].

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Chapter 3: Exploring Cardiovascular Morbidity, Complications and Sequelae

Background

Introduction - the perennial pandemic: It is being increasingly realized that the COVID-19 may have become the new reality associated with human existence world over and the mankind may have to live with it for years or even decades. Further, the grievous nature of the disease is evolving further with the genomic changes in the virus in form of mutations and evolution of variants, with enhanced infectivity and probably virulence. There are serious health, social and economic challenges being posed by the SARS-CoV-2 virus and COVID-19 as the disease.

Acute and chronic phases of COVID-19: With the ongoing research, it is apparent that apart from the advanced age and pre-existing conditions, such as diabetes, cardiovascular, pulmonary, and renal diseases, certain constituent factors render some patients more vulnerable to the more severe forms of the disease. These factors influence the COVID-19 manifestations, its course, and later the convalescence period as well as the newly defined 'Long Covid' phase. The substantial continuing morbidity after resolution of the infection indicates persisting multisystem effects of 'Long Covid'.

CV disease associated with 'Long Covid': Various clinical studies have shown that COVID-19 patients may suffer with cardiopulmonary complications like myocarditis, pericarditis, myocardial infarction, dysrhythmias, and pulmonary embolism, which may present several weeks and months after contracting the infection. The myocardial damage increases the risk of heart failure and other related complications. As such, the CV afflictions are variable with an unpredictable clinical course. Further, various long-term COVID-19 related after-effects are still unknown and may become apparent only later.

Implications for cardiac healthcare: The pandemic has considerably affected the cardiology practice with its variable spectrum of CV involvement in COVID-19 and 'Long Covid'. There has been an immense impact on the cardiac outpatient visits and working of cardiac care units and Cath labs. Simultaneously, due to fear of the infection and burden on healthcare system, the CVD patients are not able to present themselves for timely and appropriate medical advice leading to concerns about worsening of the overall CV health and higher prevalence of morbidity, complications, and mortality.

Managing the 'Long Covid's challenges: In view of the wide spectrum of CV diseases in COVID-19 and 'Long Covid' patients, there is needed to devise suitably modified healthcare methodologies. Following clinical and investigational assessment, the patients should be managed as per clinical manifestations, extent of organ damage and associated complications with the aim to prevent further organ damage. The CV manifestations are common and pose a new challenge to the healthcare providers and need to be managed with pharmacological as well as non-pharmacological modalities.

Introduction: the perennial pandemic

It is being increasingly realised that the COVID-19 may have become the new reality associated with human existence world over and the mankind may have to live with it for years or even decades [1]. Following infection, the SARS-CoV-2 virus becomes an intracellular entity, and it may not be possible to eradicate the intracellular virions. Further, while we continue to explore the agent factors, disease transmission dynamics, pathogenesis and clinical spectrum of the disease, and therapeutic modalities, the grievous nature of the disease is evolving further with the genomic changes in the virus and pathophysiological alterations and clinical manifestations of the disease.

The future of the disease, of course, is stated to depend on various known and unknown factors, many of them may not be modifiable. There are serious challenges posed by SARS-CoV-2 virus and COVID-19 as the disease that are further increased by mutations and evolution of variants with enhanced infectivity and probably virulence. The significance of viral mutations needs to be highlighted and investigated further, which may help in designing therapeutics to combat the disease as well as developing effective vaccines for its prophylaxis. In addition, the avenues for improving the immune response to the infection and following vaccine inoculation, and the immunity in general are to be explored and harnessed.

COVID-19 as acute and chronic disease

Acute COVID-19: the clinical spectrum

Being exposed to the SARS-CoV-2 virus, not all infected patients develop the disease. It may be remembered a

significant number of those get infected with the SARS-CoV-2 virus are asymptomatic. In fact, a recent systematic review has documented that at least one-third of SARS-CoV-2 infections occur in people who never develop symptoms, highlighting the substantial prevalence of asymptomatic infections [2]. The study included serologic surveys from more than 365,000 people in England and more than 61,000 in Spain. When analysed, a similar proportion of asymptomatic cases 32.4% in England and 33% in Spain was noted.

Further, for those who develop the disease, there is a large variation in disease severity, one component of which may be due to the genetic variability in the response to the virus [3]. The individual response following the SARS-CoV-2 exposure and the vulnerability of individuals to infection, and the clinical spectrum of COVID-19 is greatly variable (Figure 1).

The clinical manifestations of COVID-19 patients have been grouped into Stages I to III, based on the need for hospitalization, need for oxygen supplementation, progression to respiratory failure, and other parameters of the disease severity. Presently, considering the post-illness symptoms and manifestations, the resolution phase can be added to this, as Stage IV.

Factors influencing the disease course

Further, it is becoming clear that apart from the advanced age and pre-existing conditions, such as diabetes, cardiovascular, pulmonary, and renal diseases, certain constituent factors render some patients more vulnerable to the more severe forms of the disease, as is apparent from the rate of hospitalization of younger and apparently healthy individuals. The known factors including the constituent factors and several still unknown factors may influence the COVID-19 manifestations, its course, and later the convalescent phase as well. From the clinical perspective, knowledge of host constituent factors, including the genetic variations, could lead to improved care for patients with COVID-19 during the acute phase of the disease as well as during the resolution phase encompassing convalescence and 'long Covid' phase. The host genetic factors have been linked to the variable clinical manifestations of the disease following exposure to the virus at the individual level as well as in various population groups [4]. In fact, a model to understand several related factors such as age, associated co-morbidities and genetic factors including human genomic variants linked to COVID-19 outcomes can be conceived as a continuum from ultrarare to common (Figure 2).

The genetic factors and pathways related to COVID-19 involve specific deviations in the genes and pathways responsible for inter-individual COVID-19 susceptibility and response. To track the acute as well as long-term impact of

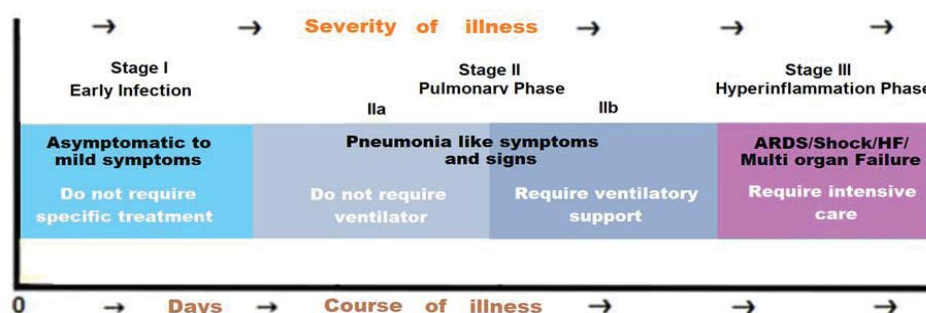


Figure 1: Clinical spectrum of COVID-19 illness. The clinical course is followed by an uneventful convalescence phase and often a phase of significantly persistent symptoms called 'Long Covid'.



Figure 2: The factors related to the disease - clinical course, convalescence, and 'Long Covid'.

the disease on health, the project called the COVID Human Genetic Effort, aims to find genetic variants that compromise the immune systems and render certain individuals more vulnerable to the risk of developing COVID-19. In addition, it aims to document the genetic variations which make some individuals resistant to the SARS-CoV2 infection [5]. In nutshell, the project aims to discover, monogenic inborn errors of immunity (IEI) underlying severe forms of COVID-19 in previously healthy individuals, monogenic variations which make certain individuals resistant to the SARS-CoV2 infection despite repeated exposure, and decipher the molecular, cellular, and immunological mechanisms by which they cause resistance to viral infection or predisposition to a severe form of the disease.

COVID-19 delayed and long-term effects

There is a growing evidence of persisting multisystem effects of COVID-19, indicating substantial continuing morbidity after resolution of the infection [6]. While most people recover quickly and completely from the virus, persistent and troubling symptoms are frequently seen and reports from cohort studies suggest that one in three people may not fully recover several weeks after initial illness and a smaller but still substantial proportion continue to have symptoms and difficulties that persist for months [7]. Further, the long-term effects of COVID-19 are seen in the younger population also, though the risk of 'Long Covid' increases with age. People who suffer with severe form of the disease, experience long-term inflammation and damage in lungs, heart, immune system, brain, the vasculature, and other organs. These long-term effects may last for months and years. The 'long Covid' is not contagious and result of the body's response to the virus infection continuing beyond the initial illness.

Most COVID-19 patients recover within few weeks without significant complications. But some patients, even those who had mild versions of the disease, including the younger people afflicted with mild or asymptomatic disease and those who did not suffer with serious disease or require hospitalization, may continue to experience symptoms after their initial recovery [8]. These patients have been described as long haulers and the clinical condition due to persisting or continuing symptoms has been called post-Covid-19 syndrome or 'Long Covid-19'. The clinical condition encompasses a delayed convalescence or recovery, persistence of symptoms, and emergence of symptoms related to the organs involved and damaged, and incapacitating complications and sequelae (Figure 3).

Often the symptoms may go un-noticed, as they are vague and nonspecific, or may persist making the patients to suffer with the COVID-19-related ordeals. Further, of various facets of the disease, this one may in due course prove to be the most difficult to deal with. The long-haul COVID patients carry their symptoms well beyond the normal course of recovery lasting for weeks and months or longer. These symptoms are often varied and relatively common and may defy a COVID-related diagnosis. Several patients who are expected to recover, continue to suffer for a variable period of weeks and months with various general symptoms such as fatigue, dizziness, memory lapses and other cognitive issues, digestive disorders, erratic heart rates, headaches, fluctuating blood pressure, and muscular and joint pains, which are often considered by the patient himself and family members as related to the weakness developed following the disease.

The older people and those with serious co-morbid medical conditions are the most likely to experience lingering COVID-19 symptoms, but even young, otherwise healthy people can continue to suffer and feel unwell for weeks to months after infection. These patients report weeks and months-long symptoms affecting various organs and given the multitude of COVID-19 cases worldwide, the prevalence of 'Long Covid' is expected to be substantial and likely to increase with the recurrent outbreaks of the disease. It is feared that the 'Long Covid' with debilitating and prolonged illness may have profound impact on health of people, their social life and livelihoods, and the economy.

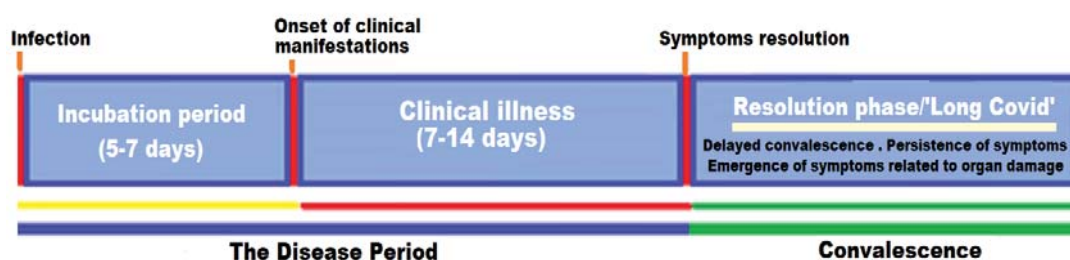


Figure 3: The abnormal convalescence or resolution phase following COVID-19 illness: delayed convalescence, persistence of symptoms, and emergence of symptoms related to organs affected, and prolonged recovery and incapacitating complications and sequelae.

The presentation of 'Long Covid' syndrome

The occurrence of persistence or appearance symptoms related to 'Long Covid' are being increasingly reported. Over the past few months evidence has mounted about the significant long-term effects of COVID-19 and it is estimated that there may be more than five million people with 'Long Covid' symptoms. The worldwide distribution of COVID-19 suggests that many of those people are currently living and experiencing the misery in the U.S. The 'long Covid' is neither well-defined nor well understood, partly because the related research is still in its infancy. The syndrome has vastly emerged from self-reporting but is a real clinical entity with the chronic health manifestations. The symptoms persist or develop outside the initial viral infection, and the duration and pathogenesis are unknown. Further, they vary from vague to severe incapacitating symptoms, and there is often a relapsing and remitting pattern.

The syndrome has been documented to affect a significant number of individuals. The etiology is likely to be multifactorial and may involve unbound immune responses, cardiopulmonary or systemic inflammation, vascular inflammation and coagulation disorders, and a direct cellular damage from viral replication during acute illness. Further, there is little known about the prevalence, risk factors, or probability to chart the protracted course early in the course of the disease. In general, the 'Long Covid' is characterized by symptoms of fatigue, headache, dyspnoea, and anosmia and likely to increase with age, higher BMI, and female sex. Further, as deciphered from various studies, experiencing more than five symptoms during the first week of illness is associated with 'Long-Covid' [9].

In a study with online survey data involving over 4,000 COVID-19 patients, about 13.3% of all ages suffered with the symptoms lasting > 28 days, whereas 10% of those aged 18-49 years had the related symptoms 4 weeks after acquiring the infection. Further 4.5% of all ages suffered with the symptoms for more than 8 weeks, and 2.3% of all ages for more than 12 weeks. The study was conducted by health-science firm Zoe Global Limited in conjunction with Biomedical Research Centre based at GSTT NHS Foundation Trust and supported by the UK Research and Innovation [10]. The analysis and inference derived from similar studies could be used to identifying individuals with 'Long-Covid' may help to reduce long-term complications and sequelae and planning health education, guidance, and rehabilitation services [11].

Diagnosis and manifestations of 'Long Covid'

As a matter of fact, medical advice should be routinely sought for all the patients having delayed recovery and persistence or emergence of symptoms. There is a multitude of adverse physical and mental health effects due to 'Long Covid' and these afflictions may last for an indefinite period. According to a study published in the Lancet, which included 1,733 people tested positive for Covid-19 and followed for 4 months, documented that more than 75% of the people who were hospitalized for COVID-19, continued to suffer with at least one symptom for 6 months after recovery. Further, it was noted that about 76% of them experienced lingering symptoms of COVID-19 long after being cured of the illness [12].

In another recent study, Carvalho-Schneider, et al. followed-up of 150 adults with only mild to moderate COVID cases for two-month and found that two thirds of them were still experiencing symptoms, most commonly shortness of breath, loss of smell and taste, and/or asthenia and fatigue [13]. Another study by Italian researchers, covering 143 COVID patients who had been discharged from the hospital, found that only about one in eight was completely free of symptoms 60 days from the beginnings of the illness [14]. The King's College London study, one of the largest surveys so far, reported that around 10 percent of patients had persistent symptoms for one month, with 1.5 to 2 percent having sustained symptoms at three months. Further, the study documented that long COVID was twice as common in women as men, and the older people, and those with more than five symptoms during their first week of illness were more likely to develop 'Long Covid' [10].

From the clinical perspective, the COVID-19 incubation period and clinical phase involves 3 weeks, the post-acute COVID can be described as the illness extending beyond three weeks from the onset of first symptoms, and the chronic COVID-19 as extending beyond 12 weeks. Around 10% of patients who have tested positive for SARS-CoV-2 virus remain unwell beyond three weeks, and a smaller proportion for further period. These patients are known as the 'long-haulers' and the persisting affliction as 'Long Covid' or 'Post-Acute Sequelae of SARS-CoV-2 infection (PASC)'. The diagnosis of the 'Long Covid' or 'Long haulers' should be entertained for various symptoms and signs linger well beyond the period of convalescence in COVID-19.

- The most common of persisting signs and symptoms of post-Covid-19 illness include: Extreme tiredness (fatigue), giddiness, paraesthesia, and joint and muscle pains

- Chest pain and tightness, palpitations, shortness of breath and Cough
- Persistence of Loss of smell or taste
- Gastrointestinal upsets such as anorexia, nausea, vomiting, diarrhoea, and stomach aches
- Headache and neurocognitive difficulties related to memory and concentration ('brain fog')
- Mental health conditions such as anxiety, insomnia, and depression, and post-traumatic stress syndrome
- Metabolic disruptions such as altered thyroid function, poor control of diabetes, etc.
- Seizures, facial paralysis, impaired vision and hearing, and tinnitus and earaches
- Skin rash like vesicular, maculopapular, urticarial, or chilblain-like lesions and hair loss

Cardiovascular disease in 'Long Covid'

Prevalence of cardiovascular involvement

COVID-19 as a disease primarily affects the lungs, as the cells in upper and lower respiratory tracts richly harbour the ACE2 receptors which are the major target of SARS-CoV-2 virus. The virus can attack and injure other organs including the heart and vasculature and cause some a multitude of symptoms. In addition, the infection can harm the immune system and those recovered, could be left with a weakened immune system and likely to be immunosuppressed and vulnerable to other infections.

The disease primarily affects adults, with odds of morbidity as well as mortality increasing both with age and the comorbidities, such as, hypertension, diabetes, coronary artery disease, and obesity. Nearly one-fourth of those hospitalized have been diagnosed with cardiovascular complications, which have been shown to contribute to roughly 40% of all COVID-19-related deaths [15]. Following recovery, the survivors may continue to suffer with long-term symptoms. The CV complications have also been described in young, previously active patients but are commoner in patients with pre-existing cardiovascular disease and may be associated with a more severe COVID-19 infection [16]. In addition, there may be an occult involvement, adding to the post-Covid cardiovascular burden [17].

Various clinical studies have shown that COVID-19 patients may suffer with cardiopulmonary complications like myocarditis, pericarditis, myocardial infarction, dysrhythmias, and pulmonary embolus, and these may present several weeks and months after contracting the infection [18]. The myocardial damage increases the risk of heart failure and other related complications [19]. Further, various long-term COVID-19 related effects are still unknown and may become apparent only later. There are concerns that the pandemic will lead to a significant surge of people battling with lasting symptoms and disabilities resulting due to the infecting virus and subsequent inflammatory process. In addition, some of the organ injury is likely to be a side effect of intensive treatments such as intubation, ventilatory therapy related and therapeutic agents used during hospitalization.

The CV involvement appears to help explain the cause of shortness of breath, palpitations, and other cardiac symptoms in 'Long Covid' patients. The imaging studies may indicate damage to myocardium weeks and months following recovery, even in those who had only mild COVID-19 symptoms. A study involving 139 healthcare workers, found that 37% of them had developed myocarditis and myopericarditis on their scans about 10 weeks after initial infection, but only half of them had related symptoms [20].

Pathogenesis of Cardiac Manifestations in COVID-19

The pathology of COVID-19 results from both direct and indirect injuries. Direct injuries are caused by infection of target cells by the virus. However, there is only limited evidence for viral entry into cardiomyocytes and SARS-CoV-2 fragments were found in interstitial cells of the myocardium with inflammatory changes [15]. Indirect injuries mainly result from immune response, inflammation reaction, circulatory dysfunction, and hypoxia. It appears that the immune-mediated hyperinflammation may play a major role in the pathophysiology of acute myocarditis associated with COVID-19. Maiese, et al. have reviewed major autopsy findings associated with CVS in COVID-19 patients from 28 published studies involving 341 cases [21]. The major findings reported are -

- Severe direct endothelial injury associated with intracellular virus,
- Multifocal necrosis, interstitial inflammatory infiltration, myocarditis, pericarditis, and myocardial hypertrophy,
- Enhanced proinflammatory response (to TNF- α , IFN- γ , CCL5, IL-6, IL-8, IL-18, etc.) in cardiovascular tissue
- Lymphocytic endotheliitis in various organs such as lung, kidney, liver, small intestine, and
- Widespread capillary thrombosis with microangiopathy and neovascularization

The mechanisms underlying the CV manifestations of COVID-19 appear to be multifactorial and both indirect and direct mechanism are likely to synergistically contribute to cardiovascular damage.

(i) ACE2-Mediated Viral Toxicity

The ACE2 receptors are expressed in the vascular system on endothelial cells, vascular smooth muscle cells, and migratory angiogenic cells, and in the heart on cardiofibroblasts, cardiomyocytes, endothelial cells, pericytes, and epicardial adipose cells. The patients with pre-existing CVD are associated with more severe COVID-19 disease, possibly because they had higher plasma levels of ACE2. As compared with the lung, the human heart has higher expression of ACE2 but much lower content of TMPRSS2, leading to diminished susceptibility in SARS-CoV-2 infection as compared to the respiratory system. Other S protein priming proteases, namely, cathepsin L and furin, are prominently expressed in the human heart, may increase its vulnerability to SARS-CoV-2.

The ACE2 receptors function as the major entry receptor for SARS-CoV-2 virus. Following priming of SARS-CoV-2 S protein by host cell proteases such as TMPRSS2, cleaves S protein at the S1/S2 and the S2' sites [22]. The cleaved S protein interacts with the ectodomain of ACE2, leading to formation of the ACE2/virus complex, which is then translocated to endosomes, where the virus is uncoated by endosomal acid protease like cathepsin L and enters into the host cells through endocytosis.

The proteolytic cleavage of ACE2 receptors from the cell surface is known as ectodomain shedding and mediated by protease enzymes, sheddase, releasing the enzymatically active ectodomain into interstitial space and circulation. There have been identified two such proteases, ADAM 17 (a disintegrin metalloprotease 17, also called TACE – tumor necrosis factor- α -converting enzyme) and TMPRSS2, which cleave ACE2 at different sites leading to two different forms of shedded ACE2 ectodomain forms, both retaining enzymatic activity [23]. It appears that the increased activity due to shedded circulating ACE2 ectoderms may have important implications for blood pressure control, cardiac function, vascular reactivity, and maintenance of cardiovascular homeostasis, contributing partly for various COVID-19 related CV effects [24].

(ii) Dysregulation of RAAS

It is known that ACE2 has certain protective roles in various organs. It converts angiotensin II (Ang II) to Ang-(1–7), and the ACE2/Ang-(1–7)/Mas axis balances the adverse impacts of RAAS, essential for preserving the physiological and pathophysiological equilibrium of the body. The interaction between SARS-CoV-2 S protein and ACE2 extracellular domains, leads to downregulation of surface ACE2 expression, resulting in enhanced Ang-II/angiotensin 1 receptor (AT1R) activity leading to comprehensive negative consequences, including aldosterone secretin, fibrosis, proinflammation, hypertrophy, vasoconstriction, enhanced reactive oxygen species and vascular permeability, cardiac remodeling, gut dysbiosis, and multiple organ dysfunctions in COVID-19. The downregulation of ACE2 expression has been seen in myocardial cells in both SARS-CoV-infected mice and humans [25]. Thus, the ACE2 downregulation and elevated levels of Ang II, both have been linked with CV complications and multiorgan failure associated with SARS-CoV-2 infection.

In addition, the studies have documented a correlation between the viral load, elevated circulating Ang II levels and organ injury in COVID-19. There have been identified several mechanisms of CV complications of the viral disease. The key role of the ACE2 as the cell receptor of SARS-CoV-2 and concerns about the safety of ACE inhibitors and AR blockers (ARBs) has been a field of investigational research for long as mechanisms regulating ACE2 expression in the pathogenesis of hypertension and cardiovascular diseases and likely impact on SARS-CoV-2 infection [26]. The use of hydroxychloroquine to block viral cell fixation has been debatable and a major therapeutic controversy [27].

(iii) Endothelial damage and thrombo-inflammation

The direct invasion of endothelial cells by SARS-CoV-2 virus and indirect damage due to inflammation and prothrombotic conditions result in vasculopathy contributing to the pathophysiological mechanisms of cardiovascular effect [28]. There is a histopathological evidence of SARS-CoV-2 viral particles in endothelial cells as well as endotheliitis indicated by activated neutrophils and macrophages in numerous organs including the lung and heart. Further, Von Willebrand factor (VWF), a coagulation glycoprotein associated with endothelial dysfunction, is significantly elevated in COVID-19 patients [29]. These events damage the endothelium and stimulate both extrinsic and intrinsic coagulation pathways, resulting in microthrombi formation and microvascular dysfunction.

(iv) Immune dysregulation-induced cytokine storm

The dysregulated immune response and uncontrolled cytokine secretion are associated with the severe COVID-19. The rapid viral replication, interference with interferon signaling, and recruitment of inflammatory cells including neutrophils, monocyte and macrophages mediate a state of hyperinflammation. In general, the reduced innate antiviral defense and unbalanced proinflammatory response contribute to severe COVID-19 illness. Following SARS-CoV-2 infection, pathogenic T helper 1 cells and inflammatory CD14+CD16+ monocytes induce high levels of granulocyte macrophage colony-stimulating factor (GM-CSF) and IL-6 expression. The elevated IL-6 has been linked to adverse prognosis and correlate with fibrinogen levels in severe COVID-19 illness [30]. The process appears to activate coagulation process, induce thrombosis, and cause endothelial dysfunction, leading to vascular leakage, tissue ischemia and hypoxia.

Analysing the data, the cardiovascular complications predominantly occur in the subgroup of severe COVID-19 illness. The pathogenesis seems to lie in hyperinflammation through disproportionate release of cytokines due to unrestrained immune activation [31]. The patients with cytokine crisis, thus, present with markedly elevated D-dimers, sepsis-induced coagulopathy (SIC) and ARDS. In addition, they are at high risk of pulmonary embolism. In children with SARS-CoV-2 infection, there are reports of cases of Kawasaki disease as an acute vasculitis of childhood, which is a major cause of acquired heart disease in children, including cardiomyopathy and coronary involvement [32].

(v) Mismatch between oxygen supply and demand

Due to involvement of lungs primarily, hypoxemia is the major manifestation of COVID-19 resulting in insufficient oxygen supply to various organs including the heart. The imbalance of oxygen supply, cytokine storm and endothelial dysfunction, are responsible for CV injury in COVID-19 illness. Further, the cytokine storm causes the release of IL-6 and catecholamines that increase core body temperature, heart rate, and cardiac oxygen consumption. Furthermore, the endothelial dysfunction and cytokine storm affect the cardiac microenvironment, leading to coronary artery spasm and thrombosis, which compromise the coronary circulation and decrease myocardial perfusion.

Severe hypoxemia, hypotension, and anemia in setting of severe COVID-19 illness, further aggravate insufficient oxygen supply. The combination of these factors causing a mismatch between oxygen demand and supply, may lead to myocardial insufficiency and damage, manifesting as type 2 MI. As compared with type 1 MI caused by plaque rupture and thrombus formation, patients with type 2 MI have higher mortality rates, due to a higher burden of acute as well as chronic multi-morbidities. In this setting, the type 2 MI is an indicator of critical COVID-19 and predictor of adverse prognosis [33].

The cardiovascular patterns in COVID-19

There has been a drop in the number of patients presenting to the cardiac outdoor facility as well as emergency department (ED) with angina and acute coronary syndromes (ACS). The management of CV conditions in the setting of COVID is encountered with various hurdles on part of the patients as well as the healthcare providers, and the interventional cardiology procedures have suffered in unprecedented manner [34]. This has resulted in delayed diagnosis and timely management of various cardiac emergencies and complications, and appropriate treatment and follow-up [35]. In the early stages of the COVID-19 pandemic, there was a dramatic increase in acute coronary syndrome and strokes happening in the community as a result of the patients fearing to visit medical facilities and neglecting their routine treatment and follow up [36]. Later and even at current stage of pandemic, there are many cardiac patients who are not keeping up with their regular treatment and may ignore symptoms pertaining to cardiac emergency.

Further, it is now well documented that the pre-existing CV disease is a major risk factor for COVID-19 related disease morbidity and mortality [37]. About one-third of admitted COVID-19 patients appear to have underlying CV disease (15%), hypertension (15%), or diabetes (20%), and have an associated increased mortality rate 10.5%, 6% and 7.3%, respectively [38]. On the other hand, cardiac manifestations in COVID-19 patients are common, and include myocarditis, cardiomyopathy, and arrhythmias either due to myocardial injury or treatment side-effects. Patients with cardiac injury are defined as having elevated troponin level. In addition, they have a higher incidence of acute respiratory disease syndrome (ARDS) and carry a higher risk of mortality [39].

Notably, the clinical presentation of acute coronary syndromes in COVID-19 patients is often atypical. In a small study, involving 18 patients with ST-segment elevation indicating potential acute myocardial infarction, 8 had obstructive coronary artery disease, whereas 10 had non-coronary myocardial injury. Among them, 4 patients died with myocardial infarction and 9 patients died with non-coronary myocardial injury [40]. Cardiac arrhythmias occurred in over 16% hospitalized patients in a Chinese cohort, and in 44% of those treated in an ICU. Heart failure is another common finding in patients admitted to ICUs and among non-survivors than among survivors [41]. Myocarditis has been associated with severe COVID-19 infection. In a series, Shi, et al. have reported that 150 patients who succumbed to the disease, death was attributable to myocarditis in 7%, and in another 33% myocarditis played a contributing role [33].

The cardiovascular manifestations in COVID-19

It has been documented that the patients with no pre-existing CV disease often have evidence of acute cardiac injury during COVID-19 illness. This may occur in young, healthy, athletic individuals who had mild or moderate symptoms. The SARS-CoV-2 infection may cause a number of clinically significant CV afflictions through various pathophysiological mechanisms. The full impact of the COVID-19 related cardiac injury and complications is yet not fully recognized. The major CV complications of COVID-19 include acute cardiac injury, acute myocardial infarction (AMI), myocarditis, arrhythmia, heart failure, shock, and venous thromboembolism (VTE)/pulmonary embolism (PE). The cardiovascular injury and complications or deterioration of coexisting CVD in setting of SARS-CoV-2 infection occur through direct or indirect mechanisms, including inflammation and cytokine crisis, direct damage due to viral invasion, dysregulation of the renin-angiotensin-aldosterone system (RAAS), endothelial cell damage, thrombo-inflammation, and oxygen supply-demand mismatch [42].

(i) Hypercoagulability, DVT and pulmonary embolism

There are associated proinflammatory and prothrombotic conditions with COVID-19 illness [43]. In fact, thromboembolic events and disseminated intravascular coagulation are associated with an adverse outcome [44]. The lower extremity deep venous thrombosis (DVT) and pulmonary embolism (PE) are commonly associated complications of COVID-19 illness. In fact, the incidence of DVT in patients with severe COVID-19 illness has ranged from 10% to 30% in various case series [45]. DVT may occur 4 to 10 days after hospitalization and about one-third of DVT cases are associated with PE [46]. In addition, SARS-CoV-2 infection can cause diffuse microangiopathy and widespread thrombosis [47].

The laboratory investigations show evidence of hypercoagulability in form of elevated D-dimer and fibrinogen levels, mild thrombocytopenia, and prolongations of prothrombin time (PT) or partial thromboplastin time (PTT). The elevated D-dimer levels (>1 g/l) are considered to be an independent predictor of in-hospital mortality [48]. There is a need of an extensive evaluation of these patients including lung scans. The patients should be treated with full-dose anticoagulation and thromboprophylaxis is recommended for all hospitalized COVID-19 patients in form of daily low-molecular-weight heparin or twice-daily unfractionated heparin [49,50]. Further, because of associated high incidence of thrombotic events, the patients are recommended extended oral anticoagulation therapy following discharge from the hospital [51].

(ii) Cardiovascular injury associated with 'Long Covid'

The CV injury is a common manifestation of COVID-19 illness [52]. It is commonly be seen de novo in course of 'Long Covid'. In a recent cohort study involving 100 COVID-19 recovered patients, 78 patients showed cardiac involvement and continuous myocardial inflammation was documented in 60 patients on cardiac MRI, regardless of pre-existing CVD or the severity of the illness [18]. The SARS-CoV-2 infection may cause non-ischemic myocardial injury, acute myocarditis, and stress-induced cardiomyopathy. Myocarditis was found to be one of the most common cardiac presentations in COVID-19 patients, as evidenced by magnetic resonance imaging (MRI) analysis [53]. The course of COVID-19-related CV manifestations including myocarditis and cardiomyopathy is variable and apart from severe disease, even those with mild or no symptoms may develop cardiomyopathy in due course (Figure 4).

COVID-19 Related Myocarditis and Cardiomyopathy

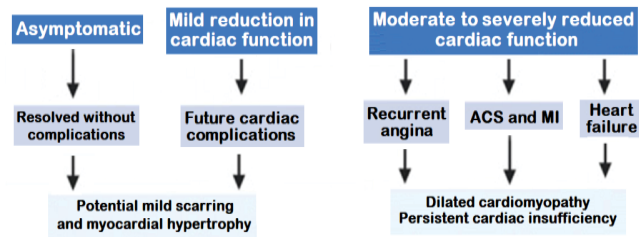


Figure 4: The CV manifestations associated with COVID-19 illness and their fallouts.

The COVID-19-related myocarditis is an inflammatory disease of the heart characterized by inflammatory infiltrates and myocardial injury *without* an ischemic cause [54]. The pathogenesis of COVID-19 associated myocarditis may lie in combination of direct cell injury and T-lymphocyte-mediated cytotoxicity, which can be augmented by the cytokine storm syndrome. Interleukin 6 (IL-6) seems to be the central mediator of cytokine storm. The cardiac injury as in myocarditis is indicated by raised cardiac troponin values, with or without reduced ejection fraction or ECG abnormalities. With a severe illness, there are raised C-reactive protein (CRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and creatinine levels. Approximately 20% of hospitalized COVID-19 patients show evidence of acute cardiac disease, in form of raised biomarkers, such as elevated troponin, which has been correlated with disease severity and mortality [55].

There are reports of fulminant myocarditis and acute coronary syndrome in COVID-19 patients with no previous CVD disease, including in professional athletes. Further, adding to uncertainty, in most of these cases the COVID-infection was mild, and the patients were not hospitalized. Four of 26 athletes from Ohio State University who suffered with mild COVID-infections showed cardiac MRI findings of myocarditis [56]. Further, though the finding of acute cardiac injury in a significant number of COVID-19 patients is not correlated with evidence of significant structural changes. In another UK study, as much as three-quarters of hospitalized patients had elevated high-sensitivity troponin but their echocardiograms demonstrated normal systolic function and no regional wall motion abnormalities [57]. Furthermore, an international patient registry of 3,000 hospitalized COVID-19 patients documented that only 2% had congestive heart failure, 0.5% had acute coronary syndrome, and 0.1% had myocarditis [58].

The COVID-19 illness is also associated with AMI due to the risk of coronary plaque rupture. In a study, newly diagnosed AMI was reported in 5.3% of cases in an electrocardiographic study of COVID-19 [59]. Another study reported it to be 2.9% based on echocardiography findings [60]. The ST-elevation myocardial infarction (STEMI) can present as the initial clinical manifestation of COVID-19, and about one-third of COVID-19 patients with were found to have non-obstructive coronary artery disease, indicating that phenomenon indicating that COVID-19 infection is associated with endothelial dysfunction as well as hypercoagulable state [61]. Further, The COVID-related acute coronary events occur most often in patients with underlying coronary artery disease and associated with compromised cardiac function and propensity for arrhythmias.

(iii) Heart failure and arrhythmias associated with COVID-19

As the cardiac injury is common with COVID-19 illness, the echocardiographic studies often reveal abnormalities like right ventricle and left ventricular diastolic dysfunction. These changes are often present with the cardiac ejection fraction in a normal range even during severe COVID illness [62]. These abnormalities and dysfunctions are characteristic of heart failure with preserved ejection fraction and appear to be due to inflammation, hypoxemia and right ventricular dilatation, pulmonary hypertension, and left ventricular diastolic dysfunction. There has also been reported an increase in incidence of stress cardiomyopathy in COVID-19 cases [63]. Further, in some cases the SARS-CoV-2 infection may lead to an indolent chronic cardiac disease [64].

The post-COVID symptoms are largely clustered as either respiratory with breathlessness or cardiac with palpitations or tachycardia. In addition, it is common for the patients recovering from COVID-19 infection to continue to have poor exercise tolerance. Some patients may not regain the normal vigour and continue to feel fatigue and low energy. For the persistent shortness of breath, an ECG, a chest X-ray, and lung scan is required for cardiopulmonary assessment. A normal chest X-ray and lung scan may exclude post-COVID lung disease, making a cardiac etiology more likely, and need

a comprehensive cardiac evaluation. In fact, a multitude of cardiac symptoms are experienced by the COVID-19 patients during convalescence, requiring comprehensive cardiopulmonary evaluation [10].

Arrhythmias have been reported in 16.7% of 138 hospitalized COVID-19 patients, with a greater proportion in ICU patients than in non-ICU patients [41]. Further, the occurrence of new-onset and or progressive arrhythmia may be the first clinical sign of cardiac involvement in COVID-19 patients [65]. The pathophysiology of origin of arrhythmias is not well established but may include direct cardiomyocyte injury, edema from pericardial infection, re-entrant arrhythmias from fibrotic scars, pro-inflammatory cytokines, and ischemia [66].

Furthermore, occurrence of various arrhythmias has a strong association with the severity of the disease. In general, Ventricular arrhythmias are higher among patients with acute cardiac injury than in patients without acute cardiac injury, whereas atrial arrhythmias are more common among patients who require mechanical ventilation than among those who did not [65]. Sudden cardiac death has been reported in COVID-19 patients who initially had only mild symptoms but who were later discovered dead at home [67]. Cardiac monitoring is advised to enable appropriate therapy for brady- and tachyarrhythmias, including atrioventricular block, and ventricular tachycardia or fibrillation. Bradyarrhythmias may require temporary cardiac pacing, and tachyarrhythmias may respond to antiarrhythmic drugs (e.g., lidocaine and mexiletine) and overdrive pacing.

A study documented presence of heart failure in 23% of indoor COVID-19 patients, which is associated with adverse prognosis [68]. Further, raised cardiac markers such as troponin and BNP/NT-proBNP were related to poor prognosis among COVID-19 patients with CV manifestations [69]. The heart failure in COVID-19 is related to cardiomyopathy and microvascular disorder, and cytokine storm. Further, as an end-stage manifestation, heart failure may be the long-term consequence of COVID-19 related cardiac affliction. The shock in setting of critical COVID-19 illness, can be cardiogenic, septic, or mixed shock. The shock has been reported in 8.7% of hospitalised COVID-19 patients, more frequently in ICU than in non-ICU patients [41].

(iv) Post-CV complications in asymptomatic COVID-19

Most of our data on post-covid cardiac injury has come from patients with severe disease who were hospitalized, which cannot be extrapolated to those who have suffered with mild or moderate illness. As such, the incidence of cardiac injury in those with asymptomatic or mild to moderate disease is not known. The pre-existing cardiovascular disorders and associated factors such as hypertension, obesity, and diabetes mellitus are likely to aggravate cardiovascular impairment during SARS-CoV-2 infection. Notably, most of these patients were leading a normal life prior to SARS-CoV-2 infection despite a compromised the cardiac physiology. The pro-coagulant effects of SARS-CoV-2 infection may increase the risk of stent thrombosis. It may lead to a thrombotic episode like DVT and PE. A meta-analysis of six published studies with over 1500 COVID-19 patients, has shown presence of cardio-vascular disease and hypertension in 16.4% and 17.1% cases, respectively [70].

As well established, asymptomatic persons account for approximately 40% to 45% of SARS-CoV-2 infections [71]. The asymptomatic patients are likely to develop several subclinical symptoms including cardiovascular manifestations. The common cardiovascular complications in these patients are significant hypotension, cardiac arrhythmia including significant sinus bradycardia and cardiomegaly. A study conducted on non-critically ill patients in Dongxihu Fangcang Hospital, China, has revealed cardiovascular diseases in 1.5% of patients, which increased to 5% during their follow-up [72]. Another study involving 100 recently recovered German patients has noted CV abnormalities in 78% of the non-hospitalised cohort with mild to moderate COVID-19 manifestations [18].

Management of 'Long Covid' syndrome

The Implications for cardiac health care

The cardiology practice has considerably been affected by the COVID-19 pandemic. It has an immense impact on cardiac outdoor routine and working of cardiac care units (CCUs) and Cath labs. The interventional procedures have come down and become restricted for various reasons. Even the procedures like stress echocardiography and trans-oesophageal echocardiography for non-invasive cardiac assessment are currently performed in less number, and fewer patients are referred to cardiac rehabilitation units and being followed-up regularly.

Concurrently, the number of patients seeking treatment for anginal episode, acute coronary syndrome, and heart

failure has come down. Astonishingly, this has been observed in areas affected as well as not affected by the COVID-19 pandemic. It appears that the patients with CVD are not presenting themselves for timely and appropriate medical advice leading to concerns about worsening of the overall cardiovascular health and higher prevalence of complications, morbidity, and mortality in those patients.

Facing the variable spectrum of cardiovascular diseases in COVID-19 and 'Long Covid' patients, there is needed to be devised suitably modified CV care methodologies. The extensive clinical work up and investigations should be accompanied with intensive follow-up in these patients. The evolving therapeutics should aim to recruit the use of innovative therapies such as interleukin inhibitors, antiviral drugs, and antibodies either from convalescent patients or synthetically designed [73].

The 'Long Covid' cardiac health care continuum

There is a Covid healthcare continuum for management of cardiac manifestations encompassing diagnostic workup, clinical follow up, investigational workup, followed by assessment of organ damage and treatment which involves pharmacological as well as non-pharmacological treatment in form of holistic care (Figure 5).

Approximately 10% of people experience prolonged illness after acute mild or severe COVID-19. Many such patients recover spontaneously with rest and gradual increase in activity, symptomatic treatment, and holistic support. Further specialized treatment is required for persistent, progressive, and newly emergent respiratory, cardiac, and neurological symptoms. As such the post-acute COVID-19 or 'Long Covid' seems to be a multisystem disease and its management is largely based on limited clinical studies and requires a whole-patient perspective [74].

The findings from various clinical and follow up studies of those infected with SARS-CoV-2 are crucial in preventing further cardiovascular damage in 'long Covid'. They are equally important for developing clinical guidelines for the care of survivors of COVID-19 afflicted with persistent and incapacitating symptoms. In a study of in unselected patients who were followed with serum troponin measurements and cardiovascular magnetic resonance imaging after a diagnosis of COVID-19, it was documented that a significant number of patients suffered with ongoing myocardial inflammation several weeks after the diagnosis [75]. The cardiac MR in the patients recently recovered from COVID-19 infection, has indicated cardiac involvement in 78% patients and ongoing myocardial inflammation in 60% patients, independent of pre-existing conditions, severity and overall course of the acute illness, and time from the original diagnosis [18]. The study, thus, outlines the need for investigations for cardiovascular involvement and prudence during the convalescent period in advising exercise and return to physical activity.

The patients with cardiac symptoms during COVID-19 illness such as chest pain, palpitations, syncope, severe breathlessness, need assessment for post-covid myocarditis and cardiomyopathy. People who did not require hospital treatment but who had symptoms during their illness suggestive of myocardial injury, such as chest pain, severe breathlessness, palpitations, symptoms or signs of heart failure, or syncope and pre-syncope, should also be assessed with a detailed clinical workup and considered for further investigations. Pulmonary embolism is associated with COVID-19 illness. Its long-term effects on pulmonary function are not currently known, but the previous studies relating to the SARS epidemic suggest persistent impairments in pulmonary function and exercise capacity in survivors. Those with respiratory symptoms such as persistent cough and breathlessness are expected to resolve after several weeks, but the progressive, non-resolving or worsening symptoms may indicate pulmonary-vascular complications such as pulmonary embolism, concomitant pneumonia, or post-inflammatory bronchoconstriction and need extensive cardiopulmonary assessment.

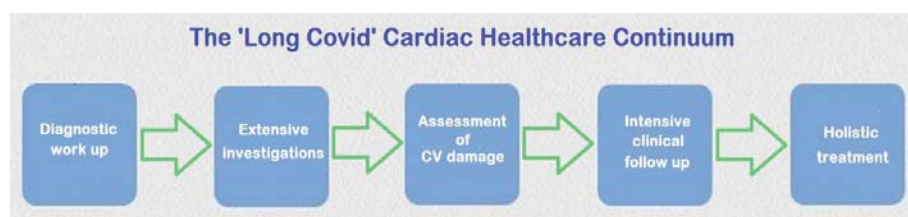


Figure 5: The 'long Covid' cardiac healthcare and management continuum – Diagnosis, Clinical follow-up, Investigations, Assessment of cardiovascular damage, and Supportive treatment.

The clinical workup and general guidelines

General clinical guidelines

Chest pain: Non-specific chest pain is common in post-acute COVID-19. It could be musculoskeletal, unexplained non-specific chest pain, or due to a cardiovascular condition. Any persistent or recurrent pain in chest in setting of post-covid convalescence requires meticulous workup.

Respiratory symptoms: A degree of breathlessness is common during acute covid-19 and convalescence. There could be worsening breathlessness and severe breathlessness may require hospitalization. In general, the breathlessness tends to improve with breathing exercises and guided pulmonary rehabilitation.

Thromboembolism: COVID-19 is an inflammatory and hypercoagulable state, with an increased risk of thromboembolic events. The hospitalized patients, in general, receive prophylactic anticoagulation followed by anticoagulant therapy after discharge in the high-risk patients for an extended period.

Ventricular dysfunction and arrhythmias: Left ventricular systolic dysfunction and heart failure can occur during post-covid period. All patients suspected with myocarditis or pericarditis should be assessed for functional status, absence of dysrhythmias, and left ventricular systolic function.

Other symptoms: Other symptoms such as anxiety, stress, and insomnia are common and may have a bearing on cardiac status and care. The elderly patients, in addition, are more prone to risk of sarcopenia and malnutrition. Depression and delirium in elderly may mask neurodegenerative disorders like Alzheimer's disease.

Investigations during 'Long Covid' Follow up

Blood tests - Anaemia should be excluded. Lymphopenia is a feature of severe, acute COVID-19 illness, whereas leucocytosis may denote infection or inflammatory response.

The biomarkers - may include C reactive protein, natriuretic peptides in heart failure, ferritin indicative of inflammation and continuing prothrombotic state, troponin suggestive of acute coronary syndrome or myocarditis and D-dimer indicating thromboembolic disease.

An ECG and Chest X Ray - at 12 weeks or earlier for new, persistent, or progressive symptoms. Cardiac echo, CT scan chest or MR scan may be required.

Further studies and research are likely to refine the indications and interpretation of diagnostic and monitoring tests in follow-up of 'Long Covid'.

Supportive treatment and rehabilitation

The 'long Covid' syndrome has multi-system involvement and unpredictable course with variable presentation depending on unmodifiable factors such as race, age and sex, and modifiable factors like comorbidities and lifestyle, and certain unknown factors. Following clinical and investigational assessment, the patients should be managed according to their clinical manifestations, extent of organ damage and associated complications. In case of suspected myocardial involvement, there is advised restriction of physical activity and periodic assessment. Both European and US guidelines advocate restrictions on exercise for three to six months in cases of myocarditis confirmed by cardiac magnetic resonance imaging or endomyocardial biopsy. An early resumption of physical activity and exercise in the presence of pulmonary dysfunction may also be associated with increased morbidity and mortality in setting of Thromboembolic Complications [76].

Activity guidance and occupational rehabilitation

Although there are no firm data on COVID-19 recovery, many reports indicate that it may takes weeks until people with even moderate infections are back to baseline. Further, SARS-CoV-2 infection may cause acute cardiac injury and an emergent cardiac evaluation is required. If the cardiac evaluation is unremarkable and there are no further cardiopulmonary symptoms, the patient can slowly and gradually resume physical activity, beginning with short walks. Current recommendations for resuming physical activity following COVID infection recommend no exercise for 2 weeks

from positive test, close monitoring for symptoms, slow resumption of exercise for asymptomatic post-COVID patients, those with Mild Post-COVID symptoms are advised rest for 2 weeks, clinical evaluation, with consideration for ECG and echocardiogram before resuming exercise, whereas those having suffered with severe COVID-19 illness need to undergo cardiac evaluation during hospitalization and 2 weeks after discharge, close monitoring and slow resumption of activity with close cardiac follow-up [77].

In general, all COVID-19 patients should be risk stratified following recovery before recommending a return to physical activity, which should be gradual, individualized, and based on subjective tolerance of the activity. It is noteworthy that apart from the severe cases and elderly, even those with mild disease and a proportion of people from all age groups may experience a prolonged recovery [78]. In general, a return to physical activity should be after at least seven days period free of symptoms, followed by two weeks of minimal exertion. As a rule, those with ongoing symptoms or history of severe COVID-19 need cardio-pulmonary assessment before advising return to physical activity [79].

Thus, in practice, for those with mild symptoms during the Covid illness and asymptomatic during convalescence period, there should be a phased return to physical activity with at least a week in between every phase (Figure 6).

The phases have been outlined as - Phase 1: Breathing exercises, mild stretching, and gentle walking. Phase 2: Low intensity walking, mild household and gardening tasks, light yoga. Phase 3: Moderate intensity aerobic and strength challenge. Phase 4: Moderate intensity aerobic and strength challenge with coordination and functioning skills. Phase 5: Return to regular exercise and physical activity pattern. Usually, a light intensity activity is advised for initial two weeks. The Borg Rating of Perceived Exertion (RPE) scale is a subjective assessment of activity and physical work and helpful in guiding the progress through the phases of increasing physical activity. The patients must rate their subjective feeling of exertion, including shortness of breath and fatigue, on a scale from 6 (no exertion at all) to 20 - maximal exertion [80].

Adjuvant and supportive therapy

Patients with 'Long Covid' suffer with symptoms due to myocarditis, cardiomyopathy, arrhythmias, heart failure, and propensity to acute coronary syndrome, myocardial infarction, and sudden death. Certain drugs may be helpful in protecting from further ongoing injury, such as Coenzyme Q10, Resveratrol, melatonin, and probiotics [81]. In severely malfunctioning heart with heart transplantation may be helpful, and regenerative medicine through stem cell therapy may hold promise.

Conclusion: Long Covid's clinical challenges

In general, levels of physical activity and exercise vary substantially across society. There are various contributing factors in the background and include cultural mores, prevailing concepts of gender, occupational demands, availability of time and cost, access and awareness for physical activity or exercise. As relates to the 'Long Covid' syndrome, the inequalities in physical activity have impact on manifestation of various symptoms including CV affliction. In turn, the overall effect of ongoing 'Long Covid' symptoms on the patient's life need to be evaluated [82].

S. N.	Activity phase	Activity details
1.	Phase One	Breathing exercises Mild stretching Gentle walking.
2.	Phase Two	Low intensity walking Mild household Gardening tasks Light yogic exercises
3.	Phase Three	Moderate intensity aerobic Moderate strength challenge
4.	Phase Four	Moderate intensity aerobic Strength challenge with coordination
5.	Phase Five	Return to regular exercise level, Regular physical activity pattern

Table 6: The phases of physical activity and exercise.

Many of those who have suffered with severe covid-19 may continue to have distressing symptoms. Symptoms specially the CV morbidity can escalate among patients with co-morbid conditions. The distressing CV 'Long Covid' symptoms are further accentuated by paucity or nonavailability of cardiac healthcare [83]. The persistent symptoms including those due to cardiovascular involvement among COVID-19 survivors pose new challenges to the healthcare providers and may be suitably managed with a combination of pharmacological and non-pharmacological treatments.

Presently, the physicians and medical communities are becoming aware of 'Long Covid' syndrome and the need of establishing post-covid clinics with multidisciplinary and integrated approach is being realized. The current guidelines are based on clinical experience and consensus. The especially designed healthcare units, such as Cardiac Covid Clinics, could be a novel concept to deal with the 'Long Covid' patients in cardiology practice and offering them specialized care and follow up.

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Chapter 4: Involvement of Gastrointestinal and Hepato-Biliary System in COVID-19 and Long Covid

Background

Introduction - GI manifestations in COVID-19: As elsewhere, the GI involvement in SARS-CoV-2 infection is mediated through abundantly expressed ACE2 cell receptors in the intestinal epithelial and hepatic cells. Following infection, the virus invades and replicates in GI tract and digestive organs. The GI manifestations include diarrhoea, nausea and vomiting, abdominal pain, and anorexia. In addition, the infection can cause altered intestinal absorbability and permeability, resulting in a malabsorption disorder. Occasionally, GI manifestations may precede respiratory symptoms or may occur without them.

Pathological mechanisms of GI involvement: The etiopathophysiology of GI and other digestive organs damage and dysfunctions in SARS-CoV-2 infection is multifactorial. It includes direct cytotoxic injury by the virus, dysregulation of RAAS and vascular injury and their fallouts, and alteration of microbiota and gut dysbiosis, and dysregulated and hyper-immune response. The hyper-inflammatory response from cytokine storm in severe COVID-19, can lead to hypoxia-induced bowel ischemia and disruption of digestive process and diarrhoea. In addition, the gut-lung axis appears to play an important role.

COVID-19 associated intestinal complications: Feeding intolerance is common in hospitalised COVID-19 patients. Ileus may occur due to multiple factors including use of sedatives and opioids given to the patients on ventilator support. Mesenteric ischemia is a serious GI complication and precipitated by hemodynamic instability and metabolic derangements compromising the blood flow. Other complications include acute colonic pseudo-obstruction, haemorrhagic colitis, and ischemic colitis. Occasionally, acute acalculous cholecystitis and acute pancreatitis in those with critical disease may occur.

The liver and biliary involvement in COVID-19: The liver is affected in 2% - 11% of patients with COVID-19. The liver damage is caused by the viral invasion of the liver cells, the immune-mediated systemic inflammatory response syndrome (SIRS), and the hepatic ischemia-reperfusion injury (HIRI). Further, the liver impairment may be partly due to hepatotoxicity due to various drugs used. In general, the hepatic involvement is common in patients with SARS-CoV-2 infection, with the Patients with severe COVID-19 suffering from a higher rate of liver damage and dysfunction than those with mild disease.

Evolving concepts related to GI involvement: The SARS-CoV-2 virus infects and multiplies in enterocytes and is shedded into the GI tract. The virus shedding from gut is more in those with diarrhoea and can occur even after respiratory clearance. The fecal-oral or fecal-respiratory virus transmission is, thus, an important issue for the disease dynamics. The PPIs may be useful in COVID-19 patients by improving gastric pH and reducing symptoms. But these drugs may increase chances for the virus entering gut from stomach and infect the enterocytes and other GI tissues and aggravate COVID-19.

Conclusion - dealing with GI manifestations: The GI manifestations are associated with elevated liver enzymes, increased prothrombin time and decreased serum albumin levels. The abdominopelvic CT scans in symptomatic COVID-positive patients may show intestinal mural thickening, abnormalities in the gallbladder and biliary system. The abdominal ultrasound may show similar findings. There being no specific treatment antacids, anti-emetics, and anti-diarrhoeal agents may provide symptomatic improvement, and nutritious diet, regular exercise and a stress-free lifestyle may be helpful.

Introduction: GI manifestations in COVID-19

Prevalence of GI manifestations in COVID-19

As per a meta-analysis about 8.9% of COVID-19 patients manifest symptoms related to the digestive system [1]. In another systematic review and meta-analysis of 35 studies, comprising of 6686 COVID-19 patients, the pooled prevalence of all gastrointestinal (GI) symptoms was 15%, with nausea and/or vomiting, diarrhoea and loss of appetite being the three most common symptoms [2]. Another study by Ramchandran et al showed that overall prevalence of GI symptoms in COVID-19 patients to be 20.6%, with nausea/vomiting in 6%, Diarrhoea in 15%, nausea/vomiting + diarrhoea in 7%, and nausea/vomiting + abdominal pain in 3% of the patients profiled in the research [3].

These prevalence rates for GI symptoms are lower than reported by several studies from the USA and China in the range of 50.5% - 61.3% [4]. In addition, the presence of GI manifestations in COVID-19 at the time of admission has not been shown to be associated with increased morbidity, hospitalization, and mortality in some studies. In this respect, an important study has indicated that the presence and prevalence of GI symptoms and elevated liver enzymes are common in COVID-19 patients but do not appear to affect morbidity, ICU admission rate, or mortality [5]. But most of the studies link the GI manifestations with enhanced morbidity, ICU admissions, assisted ventilation, and higher mortality.

In fact, there are several factors, which affect presentation of non-COVID-19 and COVID-19 patients with GI symptoms to the emergency department as well as at a non-emergency medical facility during the pandemic. The lockdown measures initiated by the governments in Austria and other countries led to a substantial reduction in admissions for various diseases including GI disorders and substantial decline in various interventional procedures including GI endoscopy [6]. Several other studies have reported a sharp decrease in the number of GI emergency endoscopic procedures, both linked to a reduction in the number of patients requiring medical attention and a reduction in the number of procedures performed in patients with GI emergencies.

Gastrointestinal manifestations in COVID-19

As elsewhere, the GI involvement in SARS-CoV-2 infection is mediated through the ACE2 cell receptors, which are richly expressed in the GI tract, especially in intestines and hepatobiliary system along with the presence of the transmembrane proteases in the intestinal epithelial and hepatic cells [7]. Thus, the intestines and hepatobiliary system are potential targets for SARS-CoV-2 infection and the virus can actively invade and replicate in GI tract and digestive organs. Further, in some COVID-19 patients SARS-CoV-2 RNA is identified in anal/rectal swabs and stool specimens, during acute phase and even after the clearance of the virus from the upper respiratory tract indicating the viral infection of GI tissues, harbouring, and active replication [8].

The COVID-19 patients mostly present with fever and respiratory symptoms, however, some patients may in addition have GI manifestations, such as diarrhoea, nausea, vomiting and abdominal pain. Occasionally, the GI symptoms in COVID-19, could be the initial symptoms preceding the respiratory manifestations [9]. In addition to symptoms like nausea/vomiting, diarrhoea, and pain in abdomen, anorexia or loss of appetite have also been reported [10]. In fact, anorexia is the most common GI symptom and present in about 26.8% of COVID-19 patients. The exact mechanism of anorexia in these patients is not known, though it may be partially related to gustatory and olfactory dysfunctions. The COVID-19 associated diarrhoea, usually non-bloody diarrhoea, is a common manifestation and often accompanied by abdominal cramps [11]. Whereas GI bleeding is one of the most frequent reasons for emergency consultation. The COVID-19 patients with GI-related symptoms or concurrent symptoms are at increased risk of hospitalization and the GI emergencies during the COVID-19 pandemic represent a challenge in clinical practice.

Hepatobiliary manifestations of COVID-19

The liver as an organ of GI system, is frequently affected in COVID-19. In addition to GI symptoms, the incidence of liver dysfunction in COVID-19 patients has been reported from 39.6% to 43.4% in various studies [12]. It is manifested mainly by elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and a slight increase in total bilirubin (TBIL) and decreased serum albumin (hypoalbuminemia) levels in COVID-19 patients. The degree of elevation of the transaminases is a marker of disease severity as well as an independent predictor of mortality [13].

In a single-center retrospective study, involving in RT-PCR +ve patients ($n = 99$), nearly 43% patients had abnormal liver profiles [14]. Decreased albumin was noted in 98% of patients, while serum levels of AST, ALT, and bilirubin were elevated in 35, 28, and 18% of patients, respectively. Similarly, in an analysis of 1,099 patients, increased levels of AST were documented in 18.2% of patients with non-severe disease and 39.4% of patients with severe disease, while increased ALT levels were observed in 19.8% of patients with non-severe disease and 28.1% of patients with severe disease [15]. In another meta-analysis, Lippi, et al. noted that hepatic factors such as elevated ALT, AST, and total bilirubin, and decreased albumin were predictive of an unfavourable course and outcome [16].

In a US cohort study of 5700 COVID-19 patients, abnormalities in ALT were observed in 2176 (39.0%) patients and AST in 3263 (58.4%) patients [17]. The patients are infected with SARS-CoV-2, typically have mildly to moderately elevated ALT and/or AST in the early stages of the disease, accompanied by a slight increase in bilirubin levels. Studies have documented that the prevalence of elevated transaminase and bilirubin is at least twice as high in severe patients as in mild and moderate patients [18].

Pathophysiology of GI SARS-CoV-2 infection

The determinants of SARS-CoV-2 infection

The SARS-CoV-2 entry into host cells is dependent on its glycosylated spike (S) protein, which exists as a trimer, with each monomer containing about 1300 amino acids, of which ~300 amino acids constitute the receptor-binding domain (RBD). The RBD is involved in recognition of ACE2 receptors and their bonding. On the part of the human host, there is abundant expression of ACE2 receptors in the glandular cells of gastric, duodenal, intestinal, and rectal epithelia but esophageal epithelium, mainly composed to stratified squamous cells, expresses scanty ACE2 receptors [19]. Consequently, in COVID-19 the gastric, duodenal intestinal, and rectal epithelia may show high intracellular viral concentration, whereas the esophageal mucosa has low intracellular viral concentration. Thus, the epithelial cells and absorptive enterocytes in small intestine and colon can be potentially invaded and infected by SARS-CoV-2, which is able to replicate in the ACE2⁺ mature enterocytes. Apart from the ACE2 receptors, the presence of proteases and other viral receptors, the host immunity, and the agent factors such as infectious and virulent virus variants, and other factors like secondary infections and certain iatrogenic factors play a role in GI manifestations of SARS-CoV-2 infection (Figure 1).

For the viral invasion and infection to occur, the S protein is cleaved at S1/S2 and S2 sites by serine proteases. The type II transmembrane serine proteases (TTSPs) TMPRSS2 and TMPRSS4, are present in the GI tissues and facilitate SARS-CoV-2 infection of human small intestinal enterocytes. Like elsewhere, the mucosa-specific serine proteases, TMPRSS2 and TMPRSS4, cleave the S protein at S1/S2 and S2 sites and enable the viral invasion and infection of ACE2⁺ intestinal epithelial cells. TMPRSS4 is greater expressed than TMPRSS2 in mature enterocytes, while TMPRSS2 is more expressed than TMPRSS4 in mucus secreting goblet cells, which are modified alimentary canal columnar epithelial cells. In short, first the SARS-CoV-2 S protein combines with ACE2 to form ACE2-virus complex, which is internalised into the host cells with the assistance of serine proteases, TMPRSS2 and TMPRSS4 [20].

Inside the host cell cytoplasm, the SARS-CoV-2 RNA is released into host cytoplasm. Thereafter, through the viral polymerase proteins, the SARS-CoV-2 RNA directs the host ribosomes to generate the negative (–)-sense genomic RNA and sub-genomic or genomic positive (+)-sense RNA, assembling later the SARS-CoV-2 nucleocapsids from genomic RNA and N proteins. Finally, other SARS-CoV-2 structural proteins such as spike (S) protein, envelope (E) protein and membrane (M) protein are synthesised in the host endoplasmic reticulum (ER). Finally, the viral RNA-N complex and S, M, and E proteins enter the endoplasmic reticulum (ER)–Golgi intermediate compartment (ERGIC) to produce new virions, to be released from the host enterocytes through exocytosis to invade and infect other cells.

The ACE2 receptors are also well expressed in cholangiocytes and hepatocytes implicating a direct SARS-CoV-2 infection [20]. In addition, the endothelial cells of the liver and bile duct express ACE2 receptors, making them a potential target for virus invasion and cellular injury. Further, as the bile duct endothelial cells express greater number of ACE2 receptors than the liver endothelial cells, thus the damage to the bile duct may indirectly lead to hepatic functional impairment.

Multiple receptors for SARS-CoV-2 infection

In general, the host cellular receptors are key determinants of virus infection and disease pathogenesis. The viruses utilize multiple receptors for attachment, cell entry, and specific tissue responses. It appears that apart from ACE2, other receptors may be involved in SARS-CoV-2 infection for ACE2 receptors alone cannot account for multi-organ tropisms

Determinants of Gastrointestinal manifestations of SARS-CoV-2 Infection
The host immunity
Expression of ACE2 and other receptors
Agent factors – mutations and variants
Other factors - Secondary infections - Iatrogenic factors

Figure 1: Determinants of GI manifestations of SARS-CoV-2 Infection..

of SARS-CoV-2. Thus, other host cell receptors seeming to mediate SARS-CoV-2 infection have been identified through various techniques. Gu, et al. using genomic receptor profiling with SARS-CoV-2 S protein as the target, have identified 12 cell surface receptors including ACE2 for SARS-CoV-2 [21]. Most of the identified receptors bind at least two S protein domains, namely, the receptor-binding-domain (RBD) and the N-terminal-domain (NTD), indicating that both are critical for virus-host interaction.

Among the other receptors, the ectopic expression of asialo-glycoprotein receptor 1 (ASGR1) or Kringle domain-containing transmembrane protein 1 (KREMEN1) has been found to enable the cellular entry of SARS-CoV-2. Further, the virus susceptibility in airway epithelial ciliated and secretory cells and immune macrophages correlates with the expression of ACE2, KREMEN1 and ASGR1 respectively, and ACE2/ASGR1/KREMEN1 together are better correlated than any individual receptor. Gu, et al. have also reported that a panel of SARS-CoV-2 receptors with diverse binding properties, biological functions, and clinical correlations or implications, including ASGR1 and KREMEN1, which can function as the alternative entry receptors [22]. Further, among these, ASGR1 and KREMEN1 can directly mediate SARS-CoV-2 infection independent of ACE2. The hypothesis of existence of the multiple host cell receptors of SARS-CoV-2 may explain the infection and invasion of multiple body organs by SARS-CoV-2 and the complex clinical manifestations of COVID-19 [23].

Etiopathophysiology of GI SARS-CoV-2 infection

The etiopathophysiology of GI and other digestive organs damage and dysfunctions in SARS-CoV-2 infection is multifactorial, and includes direct cytotoxic injury by the virus, dysregulation of RAAS and vascular injury and their fallouts, and alteration of microbiota and gut dysbiosis, culminating into dysregulated immune response and cytokine crisis (Figure 2).

The ACE2 receptors are highly expressed in intestinal epithelial cells leading to a strong possibility of intestinal involvement in SARS-CoV-2 infection resulting in direct cytopathic effect leading to various GI symptoms. This is substantiated by various studies documenting presence of SARS-CoV-2 RNA in stool specimens of infected patients. In addition, the infection can cause altered intestinal absorbability and permeability, resulting in a malabsorption disorder [24]. Following endocytosis, the positive-sense RNA hijacks cellular machinery leading to synthesis of virus specific proteins. Viral particles are then assembled and released into the GI tract. The exiting viral particles are accompanied by release of cytokines, which are responsible for GI symptoms. Further, the hyper-inflammatory response from a cytokine storm in severe COVID-19 disease, can lead to hypoxia-induced bowel ischemia and contribute to disruption of digestive process and diarrhoea.

There exists a bidirectional communication between gut and lung, termed the gut-lung axis [25]. The physiological axis may explain frequently encountered digestive symptoms in patients with COVID-19 pneumonia. On the other hand, the GI SARS-CoV-2 infection may trigger or exacerbate lung inflammation via this communication. The gut microbiota regulates the development and function of the innate and adaptive immune system and tunes the immune response to pro- and anti-inflammatory processes to maintain immune homeostasis. The alterations in the gut flora composition leading to

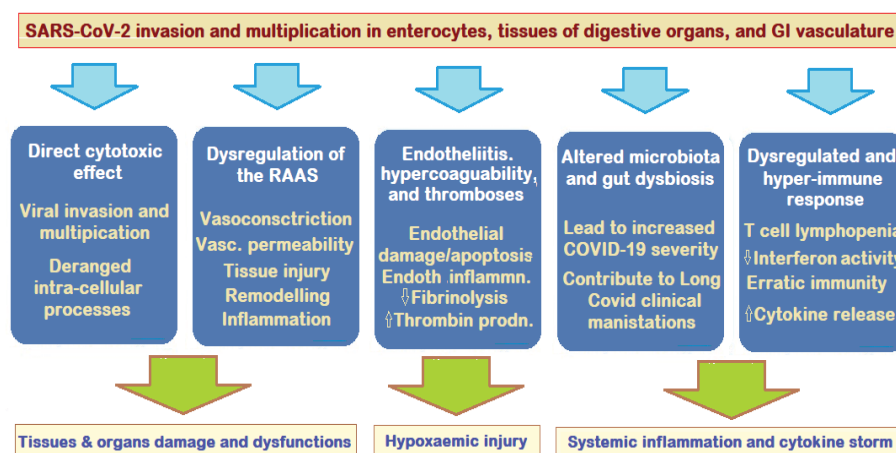


Figure 2: Factors involved in etiopathophysiology of GIT and digestive organs damage and dysfunctions in SARS-CoV-2.

microbial dysbiosis, thus, influence the respiratory tract by the common mucosal immune system and respiratory tract disease and vice versa. In addition, the viral load plays an important role in the disease severity. The higher viral loads, thus, point to a more severe disease, whereas low or decreasing viral load reflects a milder infection or recovery phase [26].

Mechanics of GI Tract SARS-CoV-2 infection

The increased ACE-2 expression in GI tissues is associated with increased susceptibility as a possible target for direct cellular toxicity. In case of severe COVID-19, SARS-CoV-2 induces the release of inflammatory cytokines IL-2, IL-7, IL-10 which are believed to be involved in the pathology. COVID-19 is a complex disease and there occurs significantly high immune response to infection and multiorgan involvement and failure, exacerbated by additional factors, such as hypovolemia, hypoxemia, sepsis, and septic shock, often accompanied by rhabdomyolysis. In addition, there can be certain other factors involved including the drug-induced GI and liver injury [27].

The potential pathophysiological mechanisms for GI system affliction and injury are multifactorial and complex compared to elsewhere (Figure 3). They include direct toxic effect of SARS-CoV-2 on enterocytes, liver, gall bladder, and pancreas; systemic inflammatory response including cytokine storm due to erratic and hyper-immune response, hypoxic-ischemic and thrombosis-reperfusion injury due to endotheliitis and vasculopathy resulting in hypercoagulability and thromboses; and virus induced gut dysbiosis and certain iatrogenic factors.

Footprints of SARS-CoV-2 infection in GI Tract

The ACE2 receptors, which are invaded by SARS-CoV-2 to enter the host cells to cause infection and direct damage are highly expressed throughout the GI tract [28]. In fact, it is reported that the ACE2 expression is approximately 100-fold higher in the GI tract (particularly the colon) than in the respiratory system [29]. Therefore, the digestive system presents a potential risk of being invaded by SARS-CoV-2. About three-quarters of critically ill patients from COVID-19 develop gastrointestinal complications, which range from self-resolving transaminitis or intestinal/colonic ileus, to acute cholecystitis or pancreatitis, and potentially life-threatening mesenteric ischemia [30]. Histological involvement of the digestive system shows numerous infiltrating plasma cells and lymphocytes as well as interstitial oedema in the lamina propria of the stomach, duodenum, and rectum [18]. In a cohort of 95 COVID-19 patients with 6 cases who underwent endoscopy examination, SARS-CoV-2 RNA was identified in the oesophagus, stomach, duodenum, and rectum from two severe COVID-19 patients, whereas only one case out of four non-severe cases were found to have SARS-CoV-2 in the duodenum [31].

SARS-CoV-2 RNA has been detected in stool and gastrointestinal tissue samples of patients with COVID-19. Guan et al analysed 62 stool samples in their study on the clinical characteristics of SARS-CoV-2 infection in China and found that four (6.5%) samples were positive for SARS-CoV-2 [14]. In other study of hospitalized COVID-19 patients, SARS-CoV-2 RNA was detected in the fecal samples from more than one-half of the patients with GI symptoms and in ~40%

Pathogenic Effects	Mechanics of Pathophysiological Involvement
Cytopathic effects of SARS-CoV-2	Virus invasion through host cell receptors on enterocytes and other GI tissues Multiplication inside enterocytes and other tissues Shedding of SARS-CoV-2 RNA and other viral particles in intestines
Gut Microbial dysbiosis	Change in gut microbial strata due to viral proinflammatory mediators Use of various antimicrobial agents Altered gut-lung axis
Inflammation and hyperinflammation	Increased and excess cytokine release (IL-2, IL-7, TNF, GM-CSF) Altered gut-lung axis Increased fecal calprotectin
Worsening of prior GI disorders	Worsening of prior irritable bowel syndrome Overexpression of ACE-2 receptors in inflamed gut in inflammatory bowel disease
Secondary infections	Increased risk of Clostridium difficile infection
Others	Viral colitis Intestinal ischaemia Altered GI epithelial integrity Altered enteric nervous system output

Figure 3: The multiple pathophysiologic Mechanisms for COVID-19-associated GIT and digestive organs injury.

of patients without any overt gastrointestinal symptoms [31]. In a meta-analysis involving 12 studies and 138 patients, the prevalence of positivity for the SARS-CoV-2 RNA in stool samples was 48.1%. Further, over 70% of the patients with positive stool samples had respiratory specimens that were negative for SARS-CoV-2 RNA, suggesting that the shedding of SARS-CoV-2 RNA in stool can significantly outlast the respiratory shedding [32].

Further, in 6 patients with GI symptoms, who underwent endoscopy and biopsy, SARS-CoV-2 RNA was detected in the tissue samples from the esophagus, stomach, duodenum, colon, and rectum. Finding high concentrations of virus RNA and the occasional detection of subgenomic mRNA in fecal cells indicate active replication in the gastrointestinal tract [33]. SARS-CoV-2 RNA has been detected in the gallbladder wall of some COVID-19 patients who underwent cholecystectomy [34]. The presence of the virus has been documented in the bile of a patient with COVID-19-related gallbladder disease [35]. SARS-CoV-2 RNA has also been detected in the fluid from pancreatic pseudocysts of COVID-19 patients [36].

GI clinical features and complications

The GI tropism, signs and symptoms

Though COVID-19 is mainly a pulmonary disease, GI symptoms and signs are present in significant number of patients. In fact, diarrhoea, nausea/vomiting, belching, anorexia, and abdominal pain are the common COVID-19 related GI symptoms. The occurrence of GI symptoms is thought to occur due to the intestinal tropism of the SARS-CoV-2 virus [14]. Based on overall pooled data, the prevalence of GI symptoms in COVID-19 in a systematic review was reported to be 18% [31]. The most common GI symptom was diarrhoea (13%), followed by nausea or vomiting (10%) and abdominal pain. Moreover, GI symptoms can coexist or even precede respiratory manifestations [37]. Rarely, COVID-19 patients can present with only GI symptoms without respiratory symptoms [11].

In a cohort study of 1141 confirmed COVID-19 patients, 183 (16%) showed gastrointestinal symptoms [38]. Other studies from various countries have also reported a varying number of gastrointestinal symptoms in COVID-19 patients. A meta-analysis found that approximately 12% out of 4805 patients with COVID-19 presented gastrointestinal symptoms [39]. Another recent study has noted the GI symptoms to be as high as 50% (39.6% - 50%) in patients with individual symptoms being nausea - 17.3%, diarrhoea - 12.9%, anorexia - 12.2%, abdominal pain - 5.8%, belching - 5%, and emesis - 5% [40].

The GI manifestations and associations

At the onset, taste disturbance is common and occurs in 71% - 88.8% of asymptomatic or presymptomatic patients with COVID-19 [41]. It can occur as complete loss (ageusia), partial loss (hypogeusia) or altered taste sensations (dysgeusia) and has been reported as an early or lone symptom of COVID-19 before involvement of the lungs or other organs. Occasionally, the GI symptoms may present earlier than fever and respiratory symptoms. In a Chinese cohort of 138 hospitalised COVID-19 patients, 14 (10.1%) patients had GI symptoms for 1-2 days before reporting fever and dyspnoea [42]. In an US study, the patients with GI symptoms were documented to be tested positive for COVID-19 more than those without GI symptoms - 61 vs. 39% [43]. Further, compared with patients without GI symptoms, patients with GI symptoms take a long time from COVID-19 onset to admission - 9.0 vs. 7.3 days [11]. Accompanying the GI manifestations in COVID-19, there are certain complications and associations in COVID-19 (Figure 4).

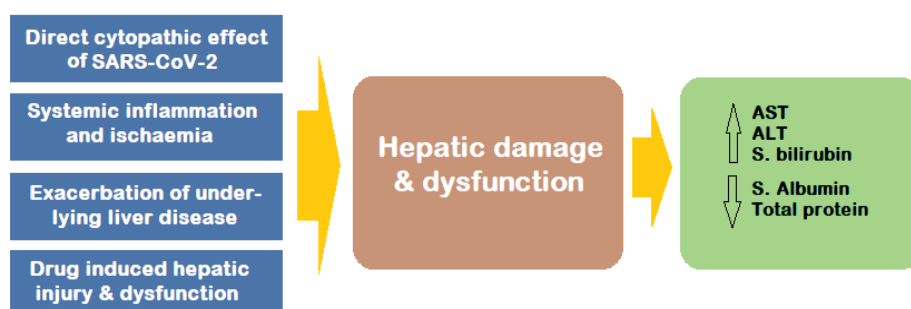


Figure 4: Transposons – the drivers of evolution.

In fact, the presence of diarrhoea and other GI symptoms has been correlated with the severity of COVID-19 and ICU admission among hospitalized patients. In a study by Zhou, et al. almost one-fourth (22.97%) of the patients with critical illness had h/o GI symptoms at initial presentation [44]. Wan, et al. also reported that COVID-19 patients with GI symptoms required more ICU care and respiratory support than those without [45]. Those with GI symptoms suffer with a greater degree of liver involvement and the incidence of acute renal insufficiency has been found to be higher in COVID-19 patients with GI symptoms than those without GI symptoms - 9.3 vs. 3.1% [46]. An important study has noted that increased level of markers of intestinal epithelial cell damage and intestinal leakage such as plasma lipopolysaccharide-binding protein (LBP)), and markers of inflammasome activation, such as IL-1 and IL-18, may promote cardiac involvement in COVID-19 patients [47].

The COVID-19 associated GI complications

Ileus is common in hospitalised COVID-19 patients and appears to be due multiple factors including high doses of sedatives and opioids given to the patients on ventilator support, which are associated with slackened intestinal function [48]. Acute colonic pseudo-obstruction is another complication and has been reported as a distinct colonic syndrome in patients with severe COVID-19, characterized by colonic gaseous distention without distal obstruction, similar to the acute colonic pseudo-obstruction, or Ogilvie's syndrome [49]. Its exact pathophysiology of intestinal pseudo-obstruction is not known, and the accompanying food intolerance may be a manifestation of prolonged critical illness. Occasionally, the colonic obstruction and distention can progress to wall necrosis and perforation [49]. A conservative line of management with electrolyte optimization, colonic decompression with a rectal tube or endoscopically is helpful and recommended. The medications that can worsen the peristalsis movement, such as, opioids, sedatives should be decreased or gradually discontinued. Haemorrhagic colitis and ischemic colitis in COVID-19 patients can occasionally occur [50,51].

Mesenteric ischemia is a serious GI complication and may occur in critically ill COVID-19 patients. The COVID-19 patients admitted to the ICU may develop mesenteric ischemia due to high doses of vasopressors, hemodynamic instability, and metabolic derangements compromising intestinal blood flow. Its incidence has been reported from 3.8% to 4% [52]. It can present as feeding intolerance, abdominal distention, increasing leukocytosis, and/or unexplained metabolic acidosis in setting of ICU. The abdominopelvic CT imaging demonstrates bowel wall thickening, pneumatosis, and/or portal venous air. There may be filling defects in the thoracoabdominal aorta or mesenteric arteries suggestive of acute thromboembolic phenomenon, or filling defects in the inferior vena cava or portomesenteric venous system. The mesenteric ischaemia can occasionally develop despite patent and well-perfusing proximal and mesenteric vessels on CT and has been termed nonocclusive mesenteric ischemia.

The terminal ileum may have areas of necrosis, extensive mucosal ulceration with areas of extensive transmural inflammation, and transmural infarction. The prothrombotic complications are attributable to the unexplained hypercoagulable state associated with COVID-19. There may be fibrin microthrombi in the capillaries underlying areas of necrosis. In fact, thrombosis of the mesenteric vasculature and the portal venous system may manifest as acute mesenteric ischemia and portal vein thrombosis respectively. The acute mesenteric ischemia is a life-threatening abdominal emergency and is associated with poor clinical outcomes. Once mesenteric ischemia is diagnosed, surgical laparotomy may be indicated for bowel examination and resection. The mortality rate of COVID-19 patients developing mesenteric ischemia is high, as much as 40%, often accompanied by multiorgan failure or refractory septic shock [53]. The other complications such as haemorrhagic colitis, severe hepatitis, pancreatic necrosis could be multifactorial in the setting of hypoxia, cytokine-induced inflammation, and hypoperfusion.

The complications related to hepatobiliary system and pancreas in association with GI involvement in COVID-19 occur, though infrequently. Presently, there is limited data on occurrence of acute pancreatitis in hospitalized with COVID-19. There have been reported incidence of acute cholecystitis in hospitalised COVID-19 patients and several cases of acute acalculous cholecystitis have been reported in patients with critical COVID-19 illness. This may be related to direct viral involvement in its pathophysiology [54]. Acute pancreatitis has also been widely reported in patients with COVID-19, especially in those with critical illness [55]. Progression to necrotizing pancreatitis may require percutaneous, endoscopic, or surgical debridement. In critically ill COVID-19 patients admitted to the intensive care unit (ICU), significant ileus and feeding intolerance occur in 46% to 56% [30].

The hepato-biliary involvement in COVID-19

Hepato-biliary manifestations in COVID-19

The liver is affected in 2% - 11% of patients with COVID-19. The hepatic comorbidities are common and 14% - 53%

cases presented with abnormal levels of alanine aminotransferase and aspartate aminotransferase (AST) during disease progression [56]. Patients with severe COVID-19 seem to have higher rates of liver involvement and dysfunction. In one of the earliest studies, Huang, et al. observed elevation of AST in eight (62%) of 13 patients in the intensive care unit (ICU) compared with seven (25%) of 28 patients who did not require care in the ICU [57]. In a large cohort study including 1099 patients from 552 hospitals in 31 provinces or provincial municipalities, more severe patients with disease had abnormal liver aminotransferase levels than did non-severe patients with disease [15]. Further, in another study, patients who had a diagnosis of COVID-19 confirmed by CT scan while in the subclinical phase (i.e., before symptom onset) had significantly lower incidence of AST abnormality than did patients diagnosed after the onset of symptoms [58]. Thus, liver injury is reported to be more prevalent in severe cases than in mild cases of COVID-19.

Liver damage in patients with hCoV infections might be directly caused by the viral invasion of the liver cells. Approximately 2% - 10% of patients with COVID-19 present with diarrhoea, and SARS-CoV-2 RNA has been detected in stool and blood samples [59]. This evidence implicates the possibility of viral exposure to the liver. Both SARS-CoV-2 and SARS-CoV bind to the angiotensin-converting enzyme 2 (ACE2) receptor to enter the target cell, where the virus replicates and subsequently infects other cells in the upper respiratory tract and lung tissue; patients then begin to have clinical symptoms and manifestations. Pathological studies in patients with SARS confirmed the presence of the virus in liver tissue, although the viral titre was relatively low because viral inclusions were not observed. As reported in patients with MERS, viral particles were not detectable in liver tissue. Gamma-glutamyl transferase (GGT), a diagnostic biomarker for cholangiocyte injury, has been reported to be elevated in 30 (54%) of 56 hospitalized COVID-19 patients [56]. Further, elevated alkaline phosphatase levels were observed in one (1.8%) of these 56 hospitalized COVID-19 patients. It has been suggested that ACE2 receptor expression is enriched in cholangiocytes, indicating that SARS-CoV-2 might directly bind to ACE2-positive cholangiocytes to dysregulate liver function [60]. Whereas pathological analysis of liver tissue from a patient who died from COVID-19 showed that viral inclusions were not observed in the liver [61].

In addition, the immune-mediated inflammation, such as cytokine storm and pneumonia-associated hypoxia, contribute to liver injury. On the other hand, the liver impairment may be partly due to hepatotoxicity due to various drugs [62]. The hepatic impairment in mild cases of COVID-19 is often transient and may return to normal in due course. However, when severe disease extensive liver damage can occur associated with immune dysfunction, lymphopenia, decreased CD4⁺ T-cells, and abnormal cytokine levels, and occasionally can lead to liver failure in critically ill COVID-19 patients.

Mechanism of hepato-biliary dysfunction

The ACE2 receptors are richly expressed both in GI epithelial cells and liver, leading to the entry through the ACE-2 receptors on hepatic endothelial cells and potential direct damage due to the cytotoxic effects of SARS-CoV-2 virus [63]. Further, the systemic inflammatory response syndrome (SIRS) caused by pneumonia may aggravate liver injury. Microscopically, the liver tissue shows mild active inflammatory lesions in the hepatic lobular portal area, which may lead to liver injury. The heightened inflammatory response to the infection is supported by the abnormally high serum levels of cytokines (serum IL-1, IL-6, IL-10) along with deranged liver profiles. It has been shown the abundant expression of ACE-2 specifically in cholangiocytes with concurrent virus binding to cholangiocytes may cause hepatic dysfunction [60].

Further, the COVID-19-induced liver injury may be closely related to SIRS. In most COVID-19 patients, the involvement is mild in the early stage but may deteriorate leading to a state of multi-organ failure. The inflammatory cytokines storm induced by an excessive immune response, the increased IL-6 and IL-10 and decreased CD4⁺ T cells, are independent risk factors for severe liver damage. High levels of IL-1 β , IL-2, IL-6, IL-8, IL-10, IL-17, interferon, IP10, and monocyte chemoattractant protein 1, triggers acute respiratory distress syndrome (ARDS) and SIRS. There is thus a vicious cycle involving lung involvement and liver injury. The activation of inflammasome-related cytokines has been related apoptosis/pyroptosis at tissue level and the COVID-19 severity and multi-organ damage as well as poor prognosis. On the other hand, COVID-19 may be considered a kind of vascular disease, with coagulopathy and thrombosis. In addition, SARS-CoV-2 may infect endothelial cells and cause diffuse endotheliitis leading to subsequent microvascular dysfunction, hypercoagulability, tissue edema, and organ ischemia [64].

As such, the histological features of GI and liver involvement in COVID-19 are non-specific. At autopsy, there is hepatomegaly with increased liver volume and enlarged gallbladder. At the tissue level, there are present mild sinusoidal dilatation, moderate microvascular steatosis, and mild lobular lymphocytic infiltration and patchy hepatic necrosis in the

periportal and centrilobular areas, apparently caused by SARS-CoV-2 infection [61]. In addition, the liver abnormalities in the COVID-19 patients may be due to liver cell dysfunction due to the pre-existing viral hepatitis or other causes such as drug toxicity and systemic inflammation [56]. The drug-induced liver injury in COVID-19 may also occur with use of the common antipyretic drug, acetaminophen. Other hepatotoxic drugs, lopinavir/ritonavir, oseltamivir, interferon, antibacterial agents may cause severe liver dysfunction in COVID-19 patients. As a matter of caution, in patients with hypohepatia, those hepatotoxic drugs should be used sparingly, combination of multiple hepatotoxic drugs must be avoided, and liver function should be monitored during their administration [27].

The hepatic ischemia–reperfusion injury (HIRI) is another underlying pathophysiological process. Its mechanism is related to reactive oxygen species, neutrophils, Kupffer cells, and calcium overload. HIRI activates Kupffer cells, neutrophils, and platelets leading to inflammation and cell injury. Simultaneously, microcirculation disorder caused by the injury of hepatic sinusoidal endothelial cells aggravates hypoxia and ischemia. Further, the hypoxic internal environment caused by severe COVID-19 can lead to ischemia, hypoxia, and reperfusion liver injury. On the other hand, the liver injury can occur in patients with hypotensive shock or severe hypoxemia. The lymphatic vessels play an important role in preventing the progression of COVID-19 by virus clearance and by absorbing and transporting the exudate produced by inflammation, inflammatory cytokines, and dead cell debris and transporting immune cells [27].

Hepatic injury and associated manifestations

ACE2 is abundantly expressed in the bile duct epithelium, about 20 times higher than in hepatocytes. The liver injury in COVID-19 may be due to the direct invasion of SARS-CoV-2 and the destruction of hepatocytes. The compensatory proliferation of liver parenchymal cells derived from bile duct cells may lead to upregulation of overall expression of ACE2 in liver tissue, further aggravating the liver injury caused by SARS-CoV-2 infection [60]. The autopsy of the liver tissue shows moderate micro-vesicular steatosis and mild lobular activity in COVID-19. There is cytopathy directly contributed by SARS-CoV-2, indicated by mitochondria swelling, endoplasmic reticulum dilatation, decrease in glycogen granules, and impaired cell membranes. Histologically, there are present numerous apoptotic hepatocytes and binuclear hepatocytes. The direct effect of SARS-CoV-2 may, thus, damage the liver and may be a key factor in liver dysfunction [63]. The current evidence supports that COVID-19-associated liver injury has multifactorial etiology including drug-induced liver injury, systemic inflammatory reaction, hypoxia ischemia reperfusion liver injury, and possible direct injury by SARS-CoV-2 to the liver.

In general, the hepatic injury is common in patients with SARS-CoV-2 infection and there are studies to suggest that the COVID-19 patients with severe disease tend to have an increased risk of developing liver damage and dysfunction [65]. As noted, the hepatic manifestations occur due to a direct cytopathic effect of the virus, associated systemic inflammation and ischaemia, exacerbation of an underlying chronic liver disorder, and due to iatrogenic factors including drug induced liver injury. The hepatic damage and dysfunctions are reflected in liver profile as elevated transaminases and serum bilirubin, and decreased albumin and total proteins (Figure 5).

The multiple organ injury, especially liver injury during COVID-19 is mainly responsible for certain special manifestations [66]. It has been observed that some patients recovered from severe COVID-19, suffer with hyperpigmentation and a darkened face and skin at other parts during recovery. The liver dysfunction appears to lead to pigmentation via three different pathways. First, liver dysfunction can hinder inactivation of estrogen and the increased estrogen level reduces the inhibition of thiamine on tyrosinase *in vivo*, thus increasing the conversion of tyrosine into melanin. Secondly, the abnormal liver function can lead to adrenocortical hypofunction, as the liver cannot metabolize the melanocyte-stimulating hormone secreted by the anterior pituitary gland, which causes increased secretion of melanin. Finally, the liver damage can increase the serum iron levels, which can lead to hyperpigmentation and darkened face [67].

Evolving concepts related to GI involvement

Theory of fecal-oral transmission of SARS-CoV-2

The main mode of transmission of the SARS-CoV-2 virus is through respiratory droplets along with prominent respiratory system involvement. However, fecal-oral transmission due to the shedding of the virus in the gastrointestinal (GI) tract have been shown to occur up to 10 weeks after respiratory clearance and may be an important factor in the disease dynamics [68]. Various studies in China and elsewhere have recognized that the fecal–oral transmission of SARS-CoV-2 is possible. Guan, et al. analysed 62 stool samples in their study on the clinical characteristics of SARS-CoV-2

The GI manifestations of SARS-CoV-2 Infection
Oral symptoms Altered taste (dysgeusia) Xerostomia Gingivitis Cheilitis Aphthous ulcers Vesiculobullous lesions
Nasopharyngeal symptoms Anosmia Nasal stuffiness
Esophageal manifestations Erosions, Ulcers Esophageal bleeding
Gastric manifestations Anorexia Nausea/vomiting GI bleeding
Intestinal manifestations Diarrhoea Abdominal pain
Colonic manifestations Colitis Diarrhoea Secondary bacterial infection e.g., <i>Cl. difficile</i> GI bleeding
Hepatobiliary manifestations Asymptomatic transaminitis Jaundice Hypoalbuminemia New onset decompensation Acute-on-chronic liver failure Cholangiopathy Acalculous cholecystitis
Pancreatic manifestations Asymptomatic raised amylase and lipase Mild pancreatitis

Figure 5: The etiopathology and manifestations of hepatic damage and dysfunction in COVID-19.

infection in China and found that 6.5% samples were positive for SARS-CoV-2 RNA [15]. Another study found that SARS-CoV-2 had the highest positive rate of fecal shedding (44.19%) in the early stage of infection, i.e., the first week of its clinical course [32]. In addition, the viral load measured from tissue samples has documented that SARS-CoV-2 virus can actively replicate in GI tissues [68]. Further, there are other studies to support that fecal–oral transmission may be a potential route of transmission of SARS-CoV-2 infection [19,69,70].

With the progression of SARS-CoV-2 infection, the positivity rate of SARS-CoV-2 virus nucleic acid detection in feces gradually decreases, with a plateau at 4–5 weeks in its clinical course [71]. In a cohort study of 59 COVID-19 patients in Hong Kong, 15 (25.4%) had gastrointestinal symptoms, while 9 (15.3%) exhibited viral RNA positive stool. The median viral load in feces of patients with diarrhoea was higher than that of patients without diarrhoea, with $5.1\log_{10}$ copies per ml in the former as compared to $3.9\log_{10}$ copies per ml in the latter [72]. Zheng, et al. collected 3497 respiratory, stool, serum, and urine samples from 96 confirmed COVID-19 patients after admission and detected SARS-CoV-2 in stool samples from 55 patients (59%). The viral load in respiratory tract samples peaks around symptom onset and gradually decreases over 1–3 weeks, with viral RNA becoming undetectable about 2 weeks after symptom onset, whereas there is evidence of viral shedding in the stool even after respiratory clearance, which may continue for up to 10 weeks after initial symptoms.

There has not been shown a significant difference in viral loads in stools between patients with mild COVID-19 and those with severe COVID-19, though the viral load is highest during the third and fourth weeks after disease onset. In general, compared with the respiratory samples, in fecal samples the duration of positivity is longer, with the peak time for the viral load later. Xio, et al. found that in their study of 73 hospitalized patients with SARS-CoV-2 infection, 39 (53.42%) were positive for SARS-CoV-2 RNA in stools, and 17 (23.29%) remained positive for SARS-CoV-2 RNA in stools even after the respiratory clearance of the virus [19]. Similarly, in another clinical cohort of 74 patients, 41 (55%) tested positive for SARS-CoV-2 RNA in fecal and respiratory samples. The average duration of positive respiratory samples was 16.7 days and 27.9 days for positive stool samples, which is 11.2 days longer than that of respiratory samples [29].

The viral RNA can remain positive in the feces in over 20% of the patients even after the rRT-PCR results are negative for the samples from respiratory tract. Thus, the viral infection through fecal–oral or fecal–respiratory transmission can occur even after respiratory clearance and needs to be considered as an important mode of the disease transmission [45,69]. Further, in this background, the presence of infectious SARS-CoV-2 in stool samples needs to be given a particular attention and the disinfection of feces and other sewage from patients with COVID-19 needs to be recommended. Furthermore, the significance of fecal–oral transmission should be realised to minimize the risk of nosocomial infection [73].

COVID-19 and the use of proton pump inhibitors

The prescription of proton pump inhibitors (PPIs) as well as their self-medication is common. While the reduction of stomach acid may be beneficial to patients with gastric disorders, it may leave the gut vulnerable to CoV infection. It has been suggested that the S protein of SARS-CoV mediates the fusion with host cells under neutral pH conditions [74]. Further, it is known that the virus can remain stable within a range of neutral near-neutral pH, but an extremely alkaline pH 12 and 14 and highly acidic pH 1 and 3 can lead to the inactivation of SARS-CoV (75). Applying the same analogy to SARS-CoV-2, upon ingestion most of the virus particles are inactivated by gastric acid. However, if a person is taking a gastric acid suppressant such as a PPI for a long period of time, the stomach acidity will decrease and the virus, SARS-CoV-2 may have an increased chance to enter the gut from the stomach and can successfully invade and infect the enterocytes and other GI tissues.

Consequent to this background, the current clinical data appear to support that the use of PPIs may facilitate SARS-CoV-2 infection and aggravate COVID-19. Further, with the higher dose of PPIs, there are significantly increased chances of a positive rRT-PCR test [76]. In fact, the use of PPIs is associated with a 79% increased risk of severe clinical outcomes of COVID-19 [77]. However, the patients taking histamine-2 receptor antagonists may not be at an elevated risk [78].

SARS-CoV-2 infection in pre-existing GI diseases

There are certain issues related to COVID-19 patients with pre-existing and chronic GI diseases. These patients may be at increased risk for severe illness due to COVID-19, due to chronic GI disease itself, comorbidities such as diabetes mellitus, malnutrition, and metabolic disorders, and the use of glucocorticoids for the chronic GI disease such as inflammatory bowel disease (IBD). The therapeutic regimen, in addition, needs to be adjusted and individualized based on the severity of infection and presence of comorbidities. The exact impact of pre-existing chronic liver disease (CLD) and its fallout on severity of COVID-19 is variable and not established [79].

Following detection of SARS-CoV-2 RNA in a stool specimen, attention has been paid to the involvement of GIT in COVID-19 [80]. According to a study which included 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals in China as of Jan 29, 2020, nausea, or vomiting, or both, and diarrhoea were reported in 55 (5.6%) and 42 (3.8%) patients [15]. In an autopsy case report of a man aged 85 years with COVID-19, segmental dilatation and stenosis in the small intestine was reported [81]. It is not known whether this finding was secondary to COVID-19 or a pre-existing gastrointestinal comorbidity. However, it is considered that COVID-19 has implications for the management of patients with pre-existing digestive diseases and the presence of GI comorbidities may be associated with adverse clinical outcome in these patients.

The studies suggest that liver injury is more prevalent in severe cases than in mild cases of COVID-19 [56]. But, so far, the studies do not associate the patients with chronic hepatitis B infection with a severe course of COVID-19 [15]. The liver abnormalities in patients with COVID-19 might be due to viral infection in liver cells but could also be due to other causes such as drug toxicity and systemic inflammation. However, the data about other underlying chronic liver conditions such as non-alcoholic fatty liver disease, alcohol-related liver disease, and autoimmune hepatitis, and their effect on prognosis of COVID-19 needs to be evaluated further. Patients with malignancy, in general, are more susceptible to infection due to their immunocompromised state due to the malignancy itself and anticancer treatments. However, whether patients with GI malignancy are more likely to be infected with SARS-CoV-2 than healthy individuals, is not known. Given the use of biologics and immunosuppressive agents, the patients with inflammatory bowel disease (IBD) may be more susceptible to SARS-CoV-2 infection. But there are not available sufficient data about these patients to infer about this issue. There have been suggested several strategies to minimise the potential risk of SARS-CoV-2 infection in patients with IBD. On the other hand, there are guidelines and recommendations about the use of immunosuppressive agents and biologics, diet, and endoscopy, and elective surgery, as well as measures for personal protection in these patients [82].

Conclusion – dealing with GI manifestations

Laboratory investigations, endoscopy, and imaging

In general, the development of GI and liver injury is related to the severity of COVID-19, with increasing severity leading to greater injury [83]. There is leukopenia to leucocytosis, with lymphopenia being the common derangement. The lower monocyte count is frequently encountered. The markers of inflammation, lactate dehydrogenase, ferritin, and CRP are raised. There are elevated liver enzymes, such as, aminotransferases – AST and ALT, gamma-glutamyl transferase, alkaline phosphatase. In general, the COVID-19 patients with digestive symptoms are more likely to exhibit elevated liver tests, such as AST and ALT, compared with patients without digestive symptoms. Analysis of stool samples in patients with GI symptoms may be positive for SARS-CoV-2 RNA.

There are elevated liver enzymes, AST and ALT, and elevated total bilirubin levels in 14.8% - 53% of the cases of COVID-19. Apart from the raised liver enzymes, there are observed longer prothrombin time and decreased serum albumin levels. In fact, the presence of hypoalbuminemia may indicate a severe infection [84]. There is elevated procalcitonin level and the derangement corresponds to severe disease [83]. The acute phase reactants, such as C-reactive protein (CRP) are raised and are responsible for clearance of pathogens through the complement system and enhanced phagocytosis. Compared to CRP, raised interleukin-6 (IL-6), is a better prognosticator for a negative outcome and its levels more than 3 times higher in patients with complicated COVID-19 indicate unfavourable prognosis [85].

The ultrasound examination of abdomen for GI related manifestations of COVID-19 or for evaluation of a pre-existing GI disease may be helpful. There have been identified ileocolic intussusception in paediatric cases of SARS-CoV-2 infection on abdominal ultrasound examination [86]. Among other investigations, the chest CT scans, which typically show bilateral ground-glass opacification with or without consolidations are helpful in defining the severity of the disease. The abdominopelvic CT scans performed on symptomatic COVID-positive patients have documented positive findings in over half cases [87]. The CT scans may show intestinal mural thickening, abnormalities in the gallbladder and biliary system including gallbladder distension, mural edema, and signs suggestive of acute cholecystitis, and biliary ductal dilation. The abdominal ultrasound may show similar findings such as gallbladder sludge, wall thickening, and pericholecystic fluid. A review study of 36 primary studies addressing the GI symptoms and radiologic manifestations of SARS-CoV-2 infection of the GI system documented nonspecific small and large bowel wall thickening and liquid stool throughout the bowel, and rare presentations such as pneumatosis intestinalis, pneumoperitoneum, and large volume ascites [88].

The endoscopic evaluation in GI patients including those with upper GI bleeding is a common and valuable procedure in current GI medical practice. The GI endoscopy, both lower and upper, and other GI Interventions are considered aerosol-generating procedures (AGPs) Further, GI endoscopy, as a diagnostic or therapeutic procedure, carries a potential risk for transmission of infections, including SARS-CoV-2. Therefore, pre-screening of patients undergoing endoscopy has been suggested. In addition, the adherence to high-level disinfection, safe distancing, and strict hand hygiene should be followed [89].

GI Involvement and overall prognosis in COVID-19

The major COVID-19 clinical features are respiratory manifestations ranging from mild upper respiratory symptoms to severe pneumonia and ARDS, but GI symptoms are also common and significantly complicate the course of the disease especially due to liver damage and intestinal dysbiosis influencing the overall prognosis. Thus, in the process of diagnosis and management, attention should be paid to the GI manifestations and the virus persisting in the GI tract which influence the immune response and its fallouts. Moreover, as SARS-CoV-2 is likely to be transmitted through the fecal-oral route, the prevention of the spread of disease through the COVID-19 patients with GI symptoms is of great concern [90].

As SARS-CoV-2 infects the human host through invasion of ACE2 in the GI tissue, the pathological mechanisms involve damage to the intestinal mucosal barrier and enhancement of production of inflammatory factors. It is conjectured that following infection of pulmonary alveolar cells by SARS-CoV-2, the effector CD4+ T cells reach the small intestine through the gut-lung axis and cause intestinal immune damage and diarrhoea. Simultaneously, the use of antibacterial and antiviral drugs can also lead to diarrhoea in these patients. Thus, treatment strategies for COVID-19 patients should be promptly adjusted according to presence of the GI manifestations. When compared with patients without GI manifestations, those with GI manifestations are more prone to suffer with fatigue, cough, and headache. Further, the blood tests show increased levels of neutrophils in these patients, and the inflammation markers, such as, C-reactive protein are also significantly increased, indicating ongoing inflammatory process.

Based on biochemical analyses, the occurrence of liver damage and dysfunction among COVID-19 patients with GI symptoms is as high as 17.57% compared with the 8.84% among those without GI symptoms [91]. Further, the incidence of ARDS in COVID-19 patients with GI symptoms is 6.76%, significantly higher than in those without GI symptoms (2.08%). Furthermore, the proportion of severe cases (25%) among patients with GI symptoms is higher than the overall proportion of severe cases (10.4%). Considering other way, as the severity of the disease increases, the GI manifestations become more obvious, which may be related to the replication of the virus in the GI tract. In fact, the COVID-19 patients in the intensive care unit have a higher frequency of GI symptoms including abdominal pain than other patients. Thus, the clinical symptomatology in COVID-19 patients with GI involvement is more significant and inflammatory process is more severe, and the complications are more common. Further, the patients with GI symptoms have a longer clinical course, propensity for Long Covid, and greater possibility of a positive test for fecal SARS-CoV-2 RNA, persisting for a longer period. The GI symptoms, in particular diarrhoea at initial presentation, are independently associated with more severe disease and poor prognosis [4]. Further, it was observed that elevated lipase levels in COVID-19 patients are strongly associated with severe disease [92]. In another study, occurrence of GI bleeding in COVID-19 patients was associated with adverse outcome [93].

The association of Long Covid with GI involvement

As well established now, the SARS-CoV-2 virus has affinity for the digestive system. In the early days of the SARS-CoV-2 pandemic, the attention was focused on respiratory symptoms and transmission, but it soon became known that the GI system is another organ preferentially involved for virus invasion and replication, and fecal-oral route is another likely avenue for the virus transmission. It was observed in the early course of the pandemic that the GI involvement was common, the conservative figures for patients being about 15% or over, often persisted after the acute phase of the infection and signalled adverse prognostic outcomes. As the frequent occurrence of GI symptoms dawned, they became indications for diagnostic evaluation for COVID-19 infection among various patients.

As per the study by Pan, et al. involving COVID-19 patients presenting at hospitals in Hubei, 50.5% of them had at least one digestive tract symptom. Further, the patients with GI involvement stayed longer in the hospital and had worse outcomes, with only 34.3% of those with digestive symptoms recovering versus 60% of patients without digestive symptoms discharged as recovered [11]. During the New York COVID-19 outbreak, in early May 2020, 22% of hospital-accessed COVID-19 patients had diarrhoea, 7% had abdominal pain, 16% had nausea, and 9% had vomiting [17]. During July 2020, the Italian physicians found that COVID-19 patients treated in-hospital had lingering symptoms, including GI manifestations, for up to 2 months after recovery from the acute phase [94].

There are lingering long-haul effects of COVID-19, the clinical syndrome called Long Covid, in several patients recovered from the acute illness. They are caused by organs damage, continuing inflammatory process, deranged immunity, disturbed microbiota, persisting virus or viral particles, and other factors. As related to the GI system, following recovery from COVID-19, a number of patients continue to suffer with GI symptoms, such as loss of appetite, altered sense of taste and smell, indigestion and flatulence, nausea and vomiting, abdominal pain, and diarrhoea (Figure 6).

Apart from other manifestations, Long Covid may be associated with escalated pre-existing GI conditions including irritable bowel syndrome (IBS) and other chronic GI problems. Further, as the virus potentially disturbs the gut microbiome, the GI milieu is disturbed leading to exacerbation of various digestive symptoms. In addition, the virus may also trigger new-onset post-viral IBS or other GI disorders. The digestive issues such as bloating, gaseousness, acidity, acid

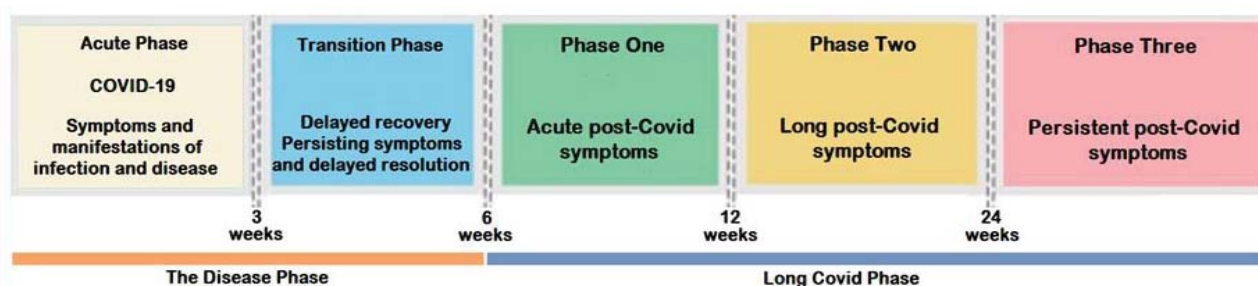


Figure 6: The GI Manifestations in Long Covid.

reflux, constipation, and exacerbation of IBS are common following recovery from COVID-19. The SARS-CoV-2 infection also disrupts the functioning of the other GI organs including the liver, pancreas, and gall bladder. Once inside the GI tract, the virus can also travel through the portal vein and may impact the vagus nerve, causing a nauseous sensation [95].

From a study of databases from the US Department of Veterans Affairs, encompassing over 73,000 patients, the researchers have identified among the COVID-19 survivors, an increased number of esophageal disorders, abdominal pain, diarrhoea, and irritable bowel syndrome, as well as increased use of laxatives, histamine receptor antagonists, and acid-suppressive medicines [96]. Further, the Long Covid can include several GI symptoms including loss of appetite, nausea, acid reflux, and diarrhoea. These can continue to plague recovered COVID-19 patients for almost three months after testing negative. According to a recent study by Weng, et al. 44% of the discharged patients had GI sequelae. As suggested by the researchers, the gastrointestinal sequelae could be because of hypoxia, related to pneumonia and ARDS associated with severe COVID-19 [97]. Some lesser common symptoms could also be signs of GI sequelae, like abdominal distention, belching, vomiting, and abdominal pain. It was also found that patients affected with GI sequelae, frequently suffered with dyspnoea, and complained about myalgias.

There is currently no specific and effective treatment for GI symptoms in COVID-19 patients. The treatment is symptomatic use of antacids, anti-emetics, and anti-diarrhoeal agents [98]. Having a good and nutritious diet, regular exercise and a stress-free lifestyle may be helpful. In addition, it is important to identify and improve the cause of diarrhoea and other symptoms and normalize microbiota and maintain intestinal microflora homeostasis. The probiotic treatment may help in improving the dysfunctional intestinal flora and repairing the damaged intestinal mucosa. The use of microecological regulators may help to maintain the intestinal microecological balance and prevent secondary bacterial infections.

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Chapter 5: Neurological and psychiatric effects of COVID-19 and Long Covid

Background

Introduction – N & P manifestations in COVID-19: COVID-19 is a multi-organ and multi-system disease, associated with high morbidity and mortality due to pulmonary and cardiovascular involvement, and attended by various neurological and psychiatric (N and P) manifestations during its acute and subsequent phases. Additionally, there is lingering anguish of long-haulers. There are certain factors which carry propensity to higher risks for neurological and psychiatric disorders in COVID-19 and post-Covid patients. In general, the severity of COVID-19 had a definite effect on subsequent N and P diagnoses.

The etiopathology of neurological involvement: Etiopathology of neurologic involvement in COVID-19 patients is diverse and multifactorial. There is no clear evidence that SARS-CoV-2 can directly invade CNS to a substantial extent and neurological involvement appears to be largely a result of dysfunctional, erratic, and overactive immune system. In severe COVID-19, systemic hypoxia occurring due to pneumonia may lead to direct damage to brain and nerve cells. The dysfunctional activity of renin-angiotensin system is another relevant mechanism affecting the disease course variously.

Footprints of N and P involvement in COVID-19: There occur wide ranging both short-term and long-term neurological manifestations and consequences during COVID-19 and post-Covid period. There are difficulties related to memory, attention, and focus, referred to as 'brain fog', persistent headaches, lingering loss of sense of smell and taste, and enduring muscle aches, accompanied by chronic fatigue. Encephalopathy, characterized by altered cerebral function ranging from mild confusion to coma, is a serious neurological manifestation associated with adverse outcomes in COVID-19.

COVID-19 associated neurological complications: There are associated prolonged prothrombin time, platelet abnormalities, elevated levels of D-dimer, increased fibrinogen/fibrin degradation products, and sepsis-induced coagulopathy. Further, COVID-19 patients with pneumonia and ARDS suffer with hypoxia, that increases risk of thrombosis by increasing blood viscosity. In addition, the systemic inflammation activates pro-coagulation mechanisms by thrombin generation and inhibiting endogenous fibrinolysis, leading to a high risk of thrombotic and cerebrovascular events.

Conclusion – dealing with N and P manifestations: The N and P manifestations in COVID-19 are variable and can emerge early or during the clinical course, or later as long-term complications. The lab investigations and neuro-imaging findings are helpful in quantifying the risk, disease course, and prognosis. In general, the N and P manifestations are dealt with in accordance with symptomatic and standard therapy practices. It should be confessed that presently our understanding about long-term N and P effects of COVID-19 and medical, psychological and rehabilitation needs of these patients is limited.

COVID-19 – a multi-organ, multi-system disease

The N and P involvement in COVID-19 and Long Covid

The SARS-CoV-2 infection leads to COVID-19, which is a multi-organ and multi-system disease. Associated with high morbidity and mortality due to pulmonary and cardiovascular involvement, the pandemic disease is attended by various neurological and psychiatric (N and P) manifestations during its acute and subsequent phases. Given that there are over 200 million confirmed cases of COVID-19 worldwide, with a conservative estimate for neurological and psychiatric symptoms, might imply that between 40,000 and 200,000 people have experienced neurological complications. The clinical studies have typically focused on hospitalized COVID-19 patients and the prevalence of neurological and psychiatric symptoms in acute phase of the disease, which could be as high as 50% or more. Additionally, there is lingering anguish of long-haulers. During the early days of COVID-19 pandemic, there were concerns about potential serious and widespread neurological and psychiatric afflictions in the acute phase and adverse outcomes for the survivors. With large number of studies now available, the milder neurological manifestations are found to be common during acute COVID-19 illness and after recovery [1]. On the other hand, the psychiatric symptoms are common in the patients from 14–90 days after SARS-CoV-2 infection than in those with several other acute illnesses [2].

In relation to the severe neurological manifestations, both ischaemic and haemorrhagic strokes have been described in COVID-19 [3]. Consistent with several studies, the risk of cerebrovascular events (ischaemic stroke and intracranial

haemorrhage) is high following SARS-CoV-2 infection, with the incidence of ischaemic stroke being as high as about one in ten (or three in 100 for a first stroke) in patients with encephalopathy. The initial alarming reports of Guillain-Barré syndrome (GBS) in relation to COVID-19 as shown in early case reports, do not seem to have borne out by large-scale epidemiological studies [4]. The concern about encephalitis lethargica cases, analogous to that linked to the 1918 influenza pandemic, has also not been proved correct. In addition, the relationship between COVID-19 and parkinsonism is equivocal and the research data on relationship of SARS-CoV-2 infection with dementia is sparse [2]. It can be inferred, based on large number of studies and meta-analyses that mild and moderate N and P manifestations are frequently encountered during the acute phase in COVID-19 patients and survivors, but serious and incapacitating neurological disorders are uncommon. Further, it may be plausible to assume that the serious neuropsychiatric sequelae such as post-encephalitic parkinsonism and new-onset dementia do not occur after COVID-19 unless the delay exceeds more than 1 year.

The incidence and prevalence of N and P afflictions

As observed in a recent retrospective cohort study using electronic health records, among 236 379 COVID-19 patients, almost in one-third of them neurological or psychiatric symptoms were reported during the 6 months period following COVID-19 diagnosis [5]. For the COVID-19 patients admitted to an ICU, the estimated incidence of a neurological or psychiatric affliction was 46.42%, as opposed to 33.62% among the overall groups. Regarding individual neurological or psychiatric manifestations in the study, the estimated incidences were 0.56% for intracranial haemorrhage, 2.10% for ischaemic stroke, 0.11% for Parkinsonism, 0.67% for dementia, and 17.39% for anxiety disorder and 1.40% for a psychotic disorder. Whereas the incidence among those with ICU admission, the figures were 6.92% for ischaemic stroke, 2.66% for intracranial haemorrhage, 0.26% for Parkinsonism, 1.74% for dementia, and 19.15% for anxiety disorder and 2.77% for a psychotic disorder, indicating that the incidence was higher in patients with severe disease. The prevalence is, thus, affected by the disease severity, intensive care unit (ICU) admission, and encephalopathy.

The study by Taquet, et al. investigated the incidence of various neurological and psychiatric outcomes in the patients 6 months after a confirmed diagnosis of COVID-19 and included ischaemic stroke, intracranial haemorrhage, parkinsonism, GBS, nerve, nerve root, and plexus disorders, myoneural junction and muscle disease, encephalitis, insomnia, mood and anxiety disorders, psychosis and dementia, and substance use disorders. There is substantial evidence for neurological and psychiatric morbidity in the patients 6 months after COVID-19 infection even in patients who did not require hospitalization. In general, the disease severity was having an obvious effect on subsequent neurological diagnoses, with the prevalence being higher in patients who had required hospitalization, and markedly so in those who had required ICU admission or suffered with encephalopathy. There is association between COVID-19 and neurodegenerative diseases like Parkinson's disease. Parkinsonism might be a delayed outcome and the data might emerge with a longer follow-up. There are concerns about post-COVID-19 parkinsonian syndromes, driven by the encephalitis lethargica. The studies support a probable association between COVID-19 and dementia and it has been noted that 2.66% of COVID-19 patients older than 65 years and 4.72% of COVID-19 patients with encephalopathy, were diagnosed with dementia within 6 months of having the disease.

Further, encephalopathy is common in critically ill patients with COVID-19. In a cohort study of 2088 patients with COVID-19 admitted to an intensive care unit, delirium was reported in 55% cases [6]. In another study of 509 hospitalized COVID-19 patients, 31.8% had encephalopathy [7]. Further, data about the incidence and outcomes associated with delirium in patients with COVID-19 is variable in different studies [8]. The estimated rates of delirium are 25% to 33% in hospitalized patients and 65% in intensive care unit (ICU) patients [9]. The acute phase of COVID-19 is followed by significant prevalence of neurological and psychiatric diagnoses over the subsequent 6 months. In fact, the association between COVID-19 and cerebrovascular events and neurodegenerative diagnoses is concerning, and probably depends on the severity and subsequent course of Long Covid. On the other hand, there is a significantly increased risk of psychiatric disorders in COVID-19 survivors. The insomnia, depression, and substance use disorders are also more common in patients with Long Covid. The neuroses as well as the psychoses following COVID-19 appear widespread and seem to persist for 6 months and beyond. Compared with neurological disorders, common psychiatric disorders (mood and anxiety disorders) show a weaker relationship with the markers of COVID-19 severity in terms of incidence.

Determinants of N & P manifestations in COVID-19

Various neurological and psychiatric manifestations and adverse outcomes occur during the acute COVID-19 illness and later. There are certain factors with carry propensity to higher risks for neurological and psychiatric disorders in

COVID-19 and post-Covid patients. In general, the severity of COVID-19 had a clear effect on subsequent neurological diagnoses. The associated risk of neurological and psychiatric outcomes is greater in patients who had required hospitalization, and markedly so in those who had required ICU admission or had developed encephalopathy, after matching propensity score for other factors, such as age or previous cerebrovascular disease (Figure 1).

Encephalopathy is common affliction in severe and critically ill COVID-19 patients and manifests as confusion, delirium, disorientation, and agitation. The encephalopathy is a risk factor as well for various neurological and psychiatric manifestations and adverse outcomes in the course of the disease. In a cohort study of 2088 patients with COVID-19 admitted to an intensive care unit, delirium was common, occurring in 55% [6]. In another study of 509 hospitalized COVID-19 patients, 31.8% had encephalopathy were older than those without encephalopathy (66 versus 55 years), had a shorter time from symptom onset to hospitalization (6 versus 7 days), more likely to be male, and more likely to have risk factors including neurologic disorder, cancer, cerebrovascular disease, chronic kidney disease, diabetes, dyslipidemia, heart failure, hypertension, or smoking [7]. Risk factors for encephalopathy included older age, history of Parkinson disease or stroke, vision impairment, and prior psychoactive medication use.

The etiology of encephalopathy in patients with COVID-19 is multifactorial. To some extent, the causes of encephalopathy are same as in other critically ill patients and include toxic metabolic encephalopathy, medication effects, cerebrovascular disease, nonconvulsive seizures, and others. Factors associated with a higher risk of delirium among patients with COVID-19 admitted to an ICU include mechanical ventilation, vasopressor use, use of restraints, benzodiazepine or continuous opioid infusions, and lack of family visitation. The patients with encephalopathy may warrant further evaluation to rule out other causes. Patients with focal or lateralizing neurologic signs on examination should be evaluated with neuroimaging. Other tests may include MRI with and without gadolinium, electroencephalography (EEG) to exclude subclinical seizures, and CSF sampling to rule out central nervous system infection.

Encephalopathy is a risk factor for poor prognosis. The hospitalized COVID-19 patients with encephalopathy stay longer and likely to have a functional impairment at hospital discharge, and a higher 30-day mortality rate compared with those without encephalopathy [7]. The neurologic dysfunction in critically ill patients may persist after the acute illness have resolved. Though, some patients with a prolonged disorder of consciousness in the setting of severe COVID-19 may later recover [10]. The long-term neurologic prognosis of COVID-19 patients with encephalopathy is not established and one-third of such patients are subjectively cognitively impaired at the time of hospital discharge, some patients may improve substantially over the subsequent weeks [11].

Pathophysiology of N and P manifestations

Pathological mechanisms of N and P involvement

The COVID-19 patients commonly present with neurological symptoms and psychiatric disorders, which are often seen in the patients with no prior psychiatric history. The etiopathology of neurologic involvement in COVID-19 patients is diverse and multifactorial, including systemic disease and inflammation, coagulopathy or hypercoagulable state, direct neuro-invasion by the virus, endotheliitis and possibly post-infectious auto-immune mechanisms. As such, the long-term effects of COVID-19 on the nervous system are uncertain, but the studies suggest that encephalopathy is associated with a worse functional outcome in hospitalized patients with COVID-19 and may have lasting effects. A study from Japan

Determinants of neurological and psychiatric manifestations in COVID-19 and Long Covid
☀ The host immunity
☀ Expression of ACE2 and other receptors
☀ Agent factors - mutations and variants
☀ Other factors - preexisting disorders - involvement of other organs - iatrogenic factors

Figure 1: Determinants of N and P manifestations in COVID-19 and Long Covid.

identified the neuronal injury as swelling and inflammation in brain tissues of a COVID-19 patient [11]. Another report by Zanin, et al., described a patient with demyelination leading to irreversible neuronal damage [12]. There can occur ischaemic stroke, brain haemorrhage and memory loss, with some patients might be suffering lifelong handicap as a result (Figure 2).

Neurological injury due to direct viral invasion - There are studies suggesting direct viral invasion of the nervous system can occur [13]. Further, there is an evidence that SARS-CoV-2 can infect neurons in the organoids, killing some and reducing the formation of synapses between them, as shown by Mesci, et al. in a preprint at bioRxiv [14]. But questions remain over the way, the virus might reach the brain [13]. In a post-mortem case series, SARS-CoV-2 particles were detected in brain specimens [15]. But these findings were unrelated to the severity of neuropathological manifestations, and it was suggested that neural injury may be due to a systemic inflammatory response triggered by the SARS-CoV-2 virus rather than the infection itself.

Autopsy studies have reported potential evidence of direct endothelial invasion by the SARS-CoV-2 virus with an associated endopheliitis and vasculopathy in lungs, heart, kidneys, liver, and small intestine [16]. Thus, suggesting the probability that the SARS-CoV-2 may directly infect the cerebral vessels, though the neuropathological studies have not confirmed frank cerebral vasculitis with SARS-CoV-2 [17]. Varatharaj, et al. analysing clinical details for 125 COVID-19 patients in the UK with COVID-19 who had neurological or psychiatric effects, found that 62% of them had evidence of damage to the cerebral blood vessels, such as strokes and haemorrhages, and 31% had altered mental states, such as confusion or prolonged unconsciousness, accompanied by swelling and inflammation of brain tissue [18]. Some of those with altered mental states later developed psychosis. A similar study published recently, compiled detailed case reports of 43 people with neurological complications from COVID-19 [19]. The most common neurological effects are stroke and encephalitis, with the latter escalating to a severe form called acute disseminated encephalomyelitis, in which both the brain and spinal cord may become inflamed and demyelinated. Less common complications include peripheral nerve damage, typical of GBS [20].

Neurological injury due to immune dysfunction - Although viruses can invade and infect the brain, there is no clear evidence that SARS-CoV-2 does so to a substantial extent. The neurological involvement in COVID-19 rather appears to be largely a result of dysfunctional, erratic, and overactive immune system. The dysregulated systemic immune response to SARS-CoV-2 infection has been implicated for, like damage to other organs, neurological injury, and dysfunctions [21,22]. There are studies to show that various neurological symptoms of COVID-19 are likely a result of widespread erratic immune response to infection rather than the virus directly infecting the brain or nervous system. The antibodies generated by the immune system against the virus appear to react with the neuronal tissues. There have been documented changes in the cerebrospinal fluid in COVID-19 patients. The injury to the nervous system or other body organs may resolve over time or cause lingering effects manifesting as Long Covid.

Cytokine Storm, leading to dysfunctional, uncontrolled, continuous activation of inflammation, may be another mechanism responsible for neurological manifestations in Covid infection. Among the inflammatory markers raised C-reactive protein (CRP) and leukocytes indicate presence of or impending cytokine storm, the release of interleukin-6 (IL-6) causes vascular leakage and activation of complement and coagulation cascades, and high levels of D-dimer signify a hypercoagulable state and endogenous fibrinolysis. These factors appear to be involved in cerebrovascular injury. In addition, several cytokines such as IL-6, IL-1 β , and TNF are secreted during the SARS-CoV-2 infection and are powerful activators of the hypothalamic-pituitary-adrenocortical (HPA) axis, which is central to the regulation of systemic immune



Figure 2: The underlying factors and neurological manifestations in COVID-19 and Long Covid.

activation and activated by blood-brain barrier dysfunction and neurovascular inflammation. The vasodilatation, hypercarbia, hypoxia, and anaerobic metabolism result in neuronal swelling, cerebral edema, and raised intracranial pressure. Thus, various inflammatory factors involved lead to proinflammatory milieu and activation of para-infectious and postinfectious triggers responsible for various neurological dysfunctions and manifestations [23].

The SARS-CoV-2 infection leads to immunosuppression and lymphopenia which leads to activation of the HPA, leading to the release of norepinephrine and glucocorticoids. In addition, it has been demonstrated SARS-CoV-2 spike (S) protein can trigger a proinflammatory response in brain endothelial cells leading to dysfunctional blood-brain barrier. The COVID-19 patients with severe disease display signs of systemic inflammation consistent with a cytokine release syndrome, such as persistent fever, elevated inflammatory markers, and elevated proinflammatory cytokines precipitating a proinflammatory state. In addition, the markers of inflammation like peripheral TNF, TNF-alpha, and IL-6 are also elevated. The proinflammatory state predisposes to endotheliitis and encephalopathy and accompanied by hyper-coagulopathy. The proinflammatory state may also be associated with thrombo-inflammation, increasing risk of stroke and other thrombotic events [24]. Complement activation may also lead to thrombotic microvascular injury in patients with severe COVID-19 [25]. The cytokine storm may also lead to brain injury by microglial activation and microglial nodules, neuronophagia and a systemic inflammatory response [26].

The occurrence of symptoms relative to initial manifestations of SAR-CoV-2 infection suggests that GBS occurs as a para-infectious rather than a post-infectious complication in most patients. In addition, there are case reports with a longer interval between the onset of viral illness and weakness, consistent with its occurrence as a post-infectious complication. Further, encephalopathy and other neurologic manifestations occur frequently in COVID-19 regardless of respiratory disease severity, indicating its immunological etiology. This is supported by a retrospective analysis involving 509 hospitalized COVID-19 patients, who presented with various neurologic manifestations including myalgias, headache, dysgeusia, anosmia, and encephalopathy. It was documented that 42% of patients had at least one neurologic symptom at onset, and 82% experienced at least one at any time during COVID-19. It was analyzed that encephalopathy correlated independently with adverse functional outcomes and higher mortality [7].

Neurological injury due to hypoxia and ischaemia - In severe COVID-19, the systemic hypoxia occurring due to pneumonia may lead to direct damage to the brain and nerve cells. In addition, hypoxemia, water and electrolyte imbalance, hormonal dysfunction, accumulation of toxic metabolites and other metabolic derangements due to multi-organ failure in severe disease, appear to play a role in encephalopathy attended by astrocytic and neuronal injury in patients with moderate to severe COVID-19. The autopsy reports have observed focal as well as global hypoxic/ischemic changes with small and large infarcts, and microglial activation with microglial nodules and neuronophagia, most prominently in the brainstem. There was scanty T lymphocyte accumulation in either perivascular regions or in the brain parenchyma, and the levels of detectable virus in brain were very low, not correlating with the histopathological lesions. These findings are suggested to result from widespread systemic inflammation and synergistic contribution from hypoxia and ischemia [27]. Further, the neuroimaging findings were consistent with a delayed post-hypoxic leukoencephalopathy and similar to those described in patients with ARDS unrelated to COVID-19 [28,29].

Neurological injury due to RAS dysfunction - The dysfunctional activity of the renin-angiotensin system (RAS) may be another relevant pathophysiologic mechanism in the neuropathogenesis. The SARS-CoV-2 S protein utilizes ACE2 receptors for the viral entry into cells. The S protein-ACE2 receptor binding leads to endotheliitis and dysfunctional endothelium to bring about inhibition of mitochondrial function and endothelial nitric oxide synthetase activity. It appears that the S protein-ACE2 receptor binding in endothelial cells increases redox stress leading to AMPK deactivation, MDM2 upregulation, and ultimately ACE2 destabilization, which exacerbate further the RAS dysregulation [30]. As the role of ACE2 within the cardiovascular and immune systems is vital to ensure homeostasis, the dysfunctional activity of the RAS leads to various secondary cardio- and cerebrovascular effects [30].

As the direct consequences of the viral S protein/ACE2 axis and damage inflicted by the immune response, there occurs downregulation of ACE2 paving the way to dysregulation of the Renin-Angiotensin-Aldosterone System (RAAS) and Kinin-Kallikrein System (KKS). The impact of dysregulation of the RAAS and KKS induced by SARS-CoV-2 infection is enormous on the cardiovascular and cerebrovascular homeostasis [31]. There are studies to suggest that the endothelial dysfunction during COVID-19 may exacerbate various deleterious events by inciting inflammatory and microvascular thrombotic processes, and pulmonary and extra-pulmonary immuno-thrombotic complications in severe COVID-19 [32]. As concerns the N and Ps manifestations, the dysfunctional RAS activity may explain various aspects of neuropathogenesis (Figure 3).

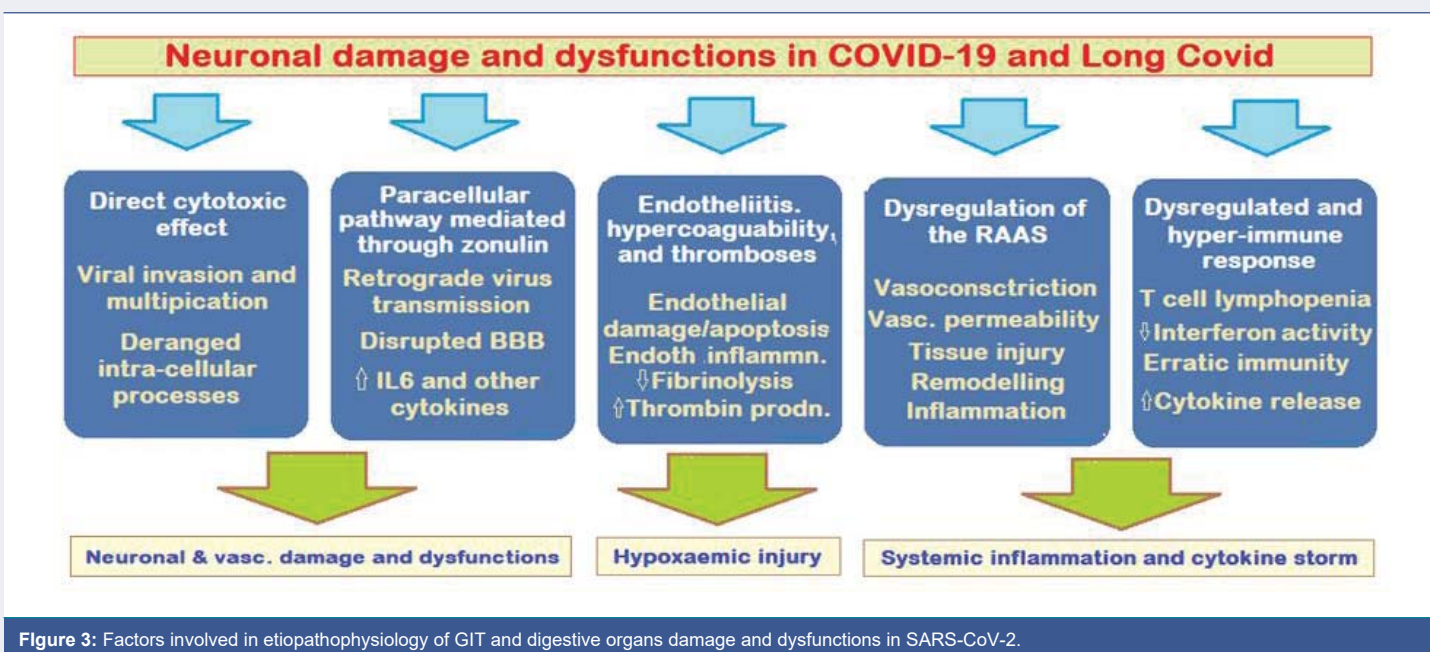


Figure 3: Factors involved in etiopathophysiology of GIT and digestive organs damage and dysfunctions in SARS-CoV-2.

Zonulin hypothesis and routes for neuro-affliction

The distinctive symptoms of the SARS-CoV2 infection, such as anosmia and dysgeusia, indicate a potential viral neurotropism and a direct route of entry into the CNS via the olfactory nerves, which may lead to viral replication and CNS invasion leading to neurological affliction and manifestations. Presently, though, there is evidence that neurological damage in COVID-19 patients is not primarily due to direct invasion of the virus into the CNS. In the majority of infected patients with severe neurological manifestations, the cerebrospinal fluid (CSF) was positive for SARS-CoV-2 RT-PCR in less than 3% of the patients [33]. In the autopsy study involving 67 people who had died of COVID-19, the virus was revealed in the brain in electron microscope, but the virus levels were low and not consistently detectable, nor were detectable in the olfactory bulbs or nearby brain regions [34]. Further, the virus or its fragments have not been significantly detected in the brain tissue, as in respiratory, cardiovascular, and GI organs, for the key reason that the expression of ACE2 receptors is scanty in brain tissues [35].

There is evidence of an increased MRI signal to the olfactory cortex suggestive of the viral infection [36]. The findings of scanty expression of ACE2 receptors in the brain tissue and increased MRI signal to the brain areas including olfactory cortex, lead us to consider that the microvascular endothelial cells with abundant expression of ACE-2 receptors are involved. The virus is likely to reach the CNS from the GI tract using the paracellular pathway to access the circulatory system and reach the brain. Such transmission may occur due to increased intestinal permeability either via the bloodstream by infecting the endothelial cells in enteric vasculature or via retrograde neuronal route through peripheral nervous system to reach trans-synaptically to brain regions. This is evidenced by the fact that GI involvement is significantly associated with the display of neurological symptoms, indicating that presence of gastrointestinal symptoms may be a risk factor for developing neurological manifestations and complications.

The zonulin hypothesis has been proposed to explain an alternate pathway for the virus entry to the nervous system in COVID-19, from the infected enterocytes. In fact, the neurological and GI symptoms are frequent in hospitalized COVID-19 patients to the tune of 54.5% and 53.2%, respectively [37]. Zonulin is a 47 KDa protein that can bind and activate the TLR4 receptors, which via MyD-88 promote proinflammatory cytokine overexpression. Zonulin, secreted to the intestinal lumen, binds PAR2 inducing the TJ disassembly of intestinal epithelial barrier (IEB). The virus, via brain zonulin receptor, induces the overexpression of zonulin, which increases BBB permeability through a similar TJ disassembly mechanism finally causing neuroinvasion. In addition, the complement system activated by zonulin, and the cytokine storm induced during viral infection potentiate the disruption of the BBB [38].

SARS-CoV-2 entry route through blood circulation - It is thought that the virus from the general circulation can pass into the cerebral circulation, where due to sluggish movement of the blood in the microcirculation the initial sites of

infection may facilitate the interaction of S protein with the ACE-2 receptors present in the microvascular endothelium. Later, the virus multiplication in the endothelial cells may lead to its further spread to the brain and brainstem areas via Virchow-Robin spaces surrounding microvasculature. The evidence is provided by experimental studies that SARS-CoV-2 can directly infect engineered human blood vessel organoids in vitro [13,14]. Further, viral-like particles have been observed in brain capillary endothelium actively crossing the endothelial cells. Thus, the haematogenous route may be the most likely route for SARS-CoV-2 to the brain. This along with the increased intestinal permeability due to overexpression of zonulin may point to entry gate for SARS-CoV-2 to reach the bloodstream or the lymphatic system, infecting endothelial cells of blood or lymphatic vessels, then is disseminating to various organs, including the CNS.

SARS-CoV-2 entry through retrograde nerve route - Among other mechanisms postulated is the retrograde spread through the vagus nerve, followed by hematogenous route. It is being considered that SARS-CoV-2 neuroinvasion may occur via the vagal afferents from the GI tract, thus involving gut-brain axis in neurological involvement in COVID-19. The enteric nervous system is interconnected with enteric glial cells, which act as antigen-presenting cells for immune cells of the gut-associated lymphoid tissue (GALT). Upon activation by viral infection, GALT initiates immune response as release of IL-6 and other inflammatory mediators, which enhance the endothelium permeability [39]. In fact, the SARS-CoV-2-related diarrhoea and the GI dysfunction may be clinical manifestations of the involvement of the enteric nervous system/enteric glial cell in the pathogenesis of GI COVID-19 [40]. Thus, the increased gut endothelium permeability gut may act as a gateway through which the virus can directly neuro-invade and find an ascending route towards the CNS through intestinal vagal afferents.

The paracellular pathway for virus transmission - The disruption by disassembling intercellular tight junctions (TJs) is an alternative route that the virus may use to enter the bloodstream and disseminate. The viruses via this pathway may disrupt epithelial or endothelial barriers including the BBB. The TJ impairment specifically occurs in severe COVID-19 patients. The zonulin hypothesis explains a correlated mechanism for brain inflammation and neuronal damage by SARS-CoV-2 virus transmission associated with increased permeability of the BBB. The high levels of the cytokine IL-6 are found in severe COVID-19 and the overexpression of zonulin may be mutually related. Zonulin regulates intestinal paracellular permeability through disassembling tight intercellular junctions and has been found to be upregulated in extraintestinal tissues such as the lung and brain tissue in patients with severe COVID-19. In severe COVID-19, zonulin is able to reach the brain tissue and enhance BBB permeability. In addition, the disruption of blood-brain barrier (BBB) due to hypoxia and hyperimmune response may facilitate neurological involvement in COVID-19 [41].

The footprints of N and P affliction in COVID-19

A wide range of both the short-term and long-term neurological manifestations and consequences have been reported during COVID-19 and post-Covid periods. There are difficulties in memory, attention, and focus, referred to as 'brain fog', persistent headaches, lingering loss of sense of smell and taste, and enduring muscle aches accompanied by chronic fatigue. The complex aspects of brain function including memory, concentration and intellect are influenced by the ongoing inflammation. Encephalopathy, which is characterized by altered mental function ranging from mild confusion to coma, is the most severe neurologic manifestation of COVID-19. There is large variation in incidence and magnitude of neurologic manifestations which been reported about 36% of hospitalized patients in China and 57% in Spain. The variation may be due to ethnic differences between the populations or the potential virus variants that are occurring over time [1].

In a study involving 509 confirmed COVID-19 patients within a hospital network in Chicago, Illinois, the neurologic manifestations were present at COVID-19 onset in 215 (42.2%), at hospitalization in 319 (62.7%), and at any time during the disease course in 419 patients (82.3%) [7]. Thus, most patients experienced a neurologic manifestation at some point while infected with COVID-19. The most common neurological manifestations included myalgias, headaches, encephalopathy, dizziness, dysgeusia, and anosmia. Other neurological pathologies, including ischemic and haemorrhagic stroke, movement disorders, focal motor and sensory deficits, ataxia, and seizures, were not common. There was reported no case of GBS or acute demyelinating encephalomyelitis. Independent risk factors for developing any neurologic manifestation were severe COVID-19 and younger age, and encephalopathy was independently associated with adverse functional outcomes and higher mortality within 30 days of hospitalization.

The results in various studies, thus, suggest that among all neurologic manifestations, encephalopathy is associated with unfavourable functional outcomes in COVID-19 hospitalized patients and persisting neurological symptoms in form

of Long Covid. A long-term follow-up is required in these patients. Even in the non-hospitalized patients with milder forms, there may occur protracted disability in form of decreased short-term memory, reduced concentration, and attention, referred to as 'brain fog', warranting further cognitive and neurological evaluations in particular cases.

N and P clinical features and complications

SARS-CoV-2 - neuro-tropism and neurological affliction

SARS-CoV-2 exhibits neurotropism and modulates immune activation and predisposes for hypercoagulation to affect brain function. The initial studies failed to document ACE2 expression in the human brain. Later, RT-PCR studies revealed low levels of ACE2 mRNA expression in the brain. Subsequent studies have revealed that ACE2 immunoreactivity is abundantly but exclusively present within brain endothelial and smooth muscle cells. In addition, scanty ACE2 expression has been found in neurons and glia. In addition to the classical symptoms of a respiratory virus disease, COVID-19 patients may present with a diversity of neurological symptoms, such as, headache, nausea, anosmia, ageusia, vomiting, myalgia/fatigue, dizziness, confusion, disorientation, impaired consciousness, and ataxia. Both myalgia and fatigue are common symptoms in COVID-19 and may be associated with a viral myositis [42]. In fact, myalgia was a common complaint in a series from Italy [43]. The COVID-19 related neurologic manifestations fall into 3 categories: central nervous system manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system manifestations (taste impairment, smell impairment, vision impairment, and nerve pain), and skeletal muscular injury manifestations. The nervous system manifestations were significantly more common in severe infections compared with non-severe infections. Further, most neurologic manifestations occur early in the illness with median time being 1-2 days (Figure 4).

The prevalence of neurologic manifestations may vary with geographical location and by patient characteristics, and most researchers have reported it to be about 50% or above. Critically ill patients have a higher proportion of neurologic complications than patients with less severe illness. The characteristic neurologic manifestations of SARS-CoV-2 infection were observed in 78 of hospitalised 214 patients with laboratory-confirmed diagnosis of COVID-19 in Wuhan. In a case series of 214 patients with coronavirus disease 2019, neurologic symptoms were seen in 36.4% of patients and were more common in patients with severe infection (45.5%) according to their respiratory status, which included acute cerebrovascular events, impaired consciousness, and muscle injury [42]. In those with severe infection, neurologic involvement was greater and included acute cerebrovascular diseases, impaired consciousness, and skeletal muscle injury. The study by Romero-Sánchez, et al. found that 57.4% of the hospitalized COVID-19 patients exhibited some kind of neurological manifestation [44]. These data are important because COVID-19 patients with neurological disorders have a higher risk of in-hospital mortality than COVID-19 patients without neurological disorders [45]. The biological variables such as sex, age, comorbid conditions like hypertension, diabetes, stress, pre-existing neurological diseases, and certain undefined genetic factors may influence the neurological manifestations during the clinical course and following recovery of COVID-19.

Anosmia and dysgeusia have been reported as common early symptoms in over 80% COVID-19 patients [46]. In

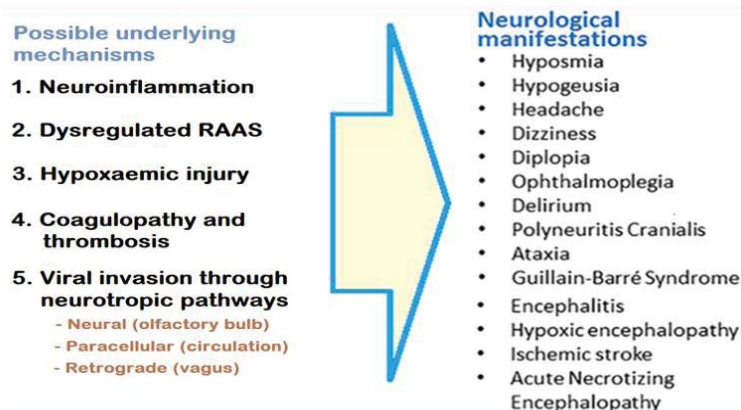


Figure 4: Contributing factors for neurological damage and dysfunctions and manifestations.

a meta-analysis involving more than 27,000 patients, olfactory dysfunction was reported in 48% cases [47]. These symptoms may be initial manifestations of COVID-19 and can occur in the absence of nasal congestion or discharge. The transient anosmia may be related to inflammatory changes in the sustentacular cells within the nasal epithelium rather than direct injury to the olfactory neurons [48]. In an MRI-based study of 20 patients with anosmia, oedematous obstruction was identified in the olfactory cleft of the nasal cavities [49]. On follow-up, olfactory function correlate with improvement of obstruction. In one series, among 33% of affected patients who had recovered olfactory function, the mean symptom duration was 8 days [46]. In a survey of non-hospitalized patients with olfactory dysfunction from Italy, 83% reported complete recovery at a mean of 37 days after symptom onset [50].

Major clinical neurological manifestations

The neurological manifestations of COVID-19 include: Encephalopathy manifesting as confusion, disorientation, ataxia, agitation, and somnolence. It may also manifest as delirium and altered consciousness due to hypoxia and other factors like sedatives, electrolyte disturbance, and MOF.

Encephalitis and meningitis manifesting as fever, altered mental state, seizures, and focal brain abnormalities.

Acute cerebrovascular disease and brain perfusion abnormalities are due to hypercoagulable states. Stroke appears to be relatively infrequent in the setting of COVID-19, with ischemic stroke being more common than intracranial haemorrhage [51]. The risk of stroke may vary according to the severity of COVID-19 and for patients with mild illness, the risk is < 1%, while for patients in intensive care, the risk may be as high as 6% [42]. There may be presence of patchy microthrombi and lacunar infarcts.

Occasionally, there may be manifestations of myelitis.

Post-infectious neurological manifestations include: The delayed effects due to dysregulated immune system affecting both the central and peripheral nervous system. There may occur acute disseminated encephalomyelitis and acute necrotizing haemorrhagic encephalopathy. Rarely, cases of GBS have been reported after COVID-19. However, a potential causal association of COVID-19 with the risk of GBS remains uncertain. A cohort study from the United Kingdom failed to show a specific association between GBS and COVID-19 infection [4]. The Miller-Fisher variant of Guillain-Barre syndrome, characterized by cranial nerve involvement, has also been reported. Rare cases of transverse myelitis and isolated peripheral neuropathies due to immune damage have also been observed. Among individual cases, a 24-year-old male infected with SARS-CoV-2 in Japan presented with meningitis, another 56-year-old male was diagnosed with encephalitis, a 29-year-old woman presented with a left temporoparietal haemorrhagic venous infarction with transverse sigmoid sinus thrombosis, and a 61-year-old woman presenting with acute weakness in both legs and progressive fatigue was diagnosed as a case of GBS.

Neuropsychiatric manifestations in COVID-19 include: The hospital stay in isolation or home isolation for prolonged durations with limited social interaction and loss of freedom, may result in anger, fear, restlessness, and irritability, negatively impact psychological wellbeing leading to depression, anxiety, fear, and loneliness, and can precipitate post-traumatic stress disorder. The COVID-19 patients under intensive care showed signs of delirium with confusion (65%), agitations (69%), and altered consciousness (21%), while 33% showed dysexecutive syndrome at discharge [1]. Thus, the psychiatric evaluation of patients is required during hospitalization and following discharge. The acute stress can activate immune system responses via amplification of the corticotropin-releasing factor system that regulates impulsivity and releases pro-inflammatory cytokines such as IL-6 and TNF- α that evoke behavioral changes aimed to protect self from injury or harm. The cytokine storm also activates the sympathetic system aggravating release of pro-inflammatory cytokines.

The autonomic nervous system related manifestations: There is evidence that the SARS-CoV-2 infection disrupts the ANS, which is either virus-mediated or immune-mediated. The patients with chronic infection present with orthostatic hypotension, vasovagal syncope, and postural orthostatic tachycardia syndrome. There can occur tachycardias, chest pain, and breathlessness due to the abnormal release of epinephrine and norepinephrine leading to orthostatic intolerance syndrome. There have been found autoantibodies to muscarinic receptors and α/β adrenoreceptors capable to cause autonomic disorders. Further, the virus itself can give rise to immune-mediated neurological syndromes [52]. In addition, hypovolaemia resulting from severe illness and high levels of catecholamine due to prolonged bed rest can result in paradoxical vasodilation, sympathetic withdrawal, and activation of the vagus nerve which cause hypotension, dizziness, and syncope.

Pre-existing neurological disease related manifestations: COVID-19 may have an impact on pre-existing neurodegenerative conditions such as Parkinson's disease and dementia. The potential impact of neurotropism of SARS-CoV-2 may have a detrimental consequence in such cases. The COVID-19 patients with pre-existing neurological deficits from stroke also have a greater risk of ICU admission, and high morbidity and mortality. These patients are at high risk of developing thrombo-embolic events and new cerebrovascular events secondary to thrombotic microangiopathy and hypercoagulability. In the patients with Parkinson's disease secondary infection, exacerbated anxiety, and poor adherence and medication errors may lead to worsening of symptoms and hospitalization.

The COVID-19-related N and P complications

Coagulopathies associated neurological manifestations: SARS-CoV-2 infection is associated with prolonged prothrombin time, platelet abnormalities, elevated levels of D-dimer, increased fibrinogen/fibrin degradation products, and sepsis-induced coagulopathy, a form of disseminated intravascular coagulation [53]. The patients with severe COVID-19 suffer with hypoxia, that increases thrombosis via activation of hypoxia-inducible transcriptional regulation and by increasing blood viscosity [54]. Thus, there occur complications associated with coagulopathy, such as venous thromboembolism, acute coronary syndrome, myocardial infarction, and cerebral infarction [55,56]. The systemic inflammation and coagulopathy are intricately linked processes. The systemic inflammation activates coagulation mechanisms by driving tissue factor-mediated thrombin generation and inhibiting endogenous fibrinolysis. In turn, activation of the coagulation system may influence inflammatory activity and contribute toward the development of haemorrhagic manifestations and thrombotic microangiopathy. There is, thus, a high risk of ischemic strokes especially in the elderly, potentially via modulation of the coagulation cascade and exacerbation of the post-stroke inflammatory response [57,58]. The risk of cerebrovascular events, both ischaemic stroke and intracranial haemorrhage, is elevated after COVID-19, with the incidence of ischaemic stroke rising to almost one in ten (or three in 100 for a first stroke) in COVID-19 patients with encephalopathy [5].

The risk factors and associated co-morbid conditions: An elevated neutrophil-to-lymphocyte ratio is an independent risk factor for mortality in hospitalized COVID-19 patients [59]. The elevated neutrophil counts are associated with ocular dysfunction during SARS-CoV-2 infection [60]. The elevated neutrophil count leading to extracellular trap formation has been associated with microvascular occlusion and cerebral hypoperfusion after acute brain injury in both mice and humans [61]. Several co-morbidities associated with neurological dysfunction, including obesity, high body mass index, diabetes, and hypertension correlate with increased rates of infection and worsen the outcomes [62-65]. Myasthenia gravis patients may display a more severe COVID-19 illness [66]. Worsening of neurological symptoms in multiple sclerosis (MS) patients with SARS-CoV2 infection has reported [67]. The SARS-CoV-2 virus invades the ACE2 receptors on the surface of endothelial cells causing the micro-vessels to become thin, weak, and leaky with propensity to microbleeds resulting in multiple small areas of damage. In addition, hypoxia can also cause leaky blood vessels.

Uncommon neurological complications of COVID-19: There are certain isolated case reports for the rare complications like viral and apparent autoimmune meningoencephalitis in patients with COVID-19. The para-infectious complications including brainstem encephalitis or isolated cerebellitis have been reported in adults and paediatric COVID-19 patients. Rarely, a few cases of acute disseminated encephalomyelitis, acute haemorrhagic necrotizing encephalopathy and myelitis with or without brain involvement have been described. Further, a not so uncommon multisystem inflammatory syndrome in children with COVID-19 presenting with neurocognitive symptoms like headache, lethargy, confusion can occur.

The N and P manifestations of Long Covid

Prevalence of N and P manifestations in Long Covid

The post-acute sequelae of COVID-19 (PASC) or Long Covid is a long-lasting disorder that arises following infection with SARS-CoV-2. The patients report a large number of symptoms, such as fatigue, dry cough, shortness of breath, headaches, and muscle aches. Davis, et al. have reported as many as 205 symptoms in a study of over 3,500 people [68]. The most common symptoms reported were fatigue, post-exertional malaise, and cognitive dysfunction. Further, these symptoms may fluctuate, and people often go through phases of feeling of improvement and relapse [69]. With multiple symptoms related to various organs, it seems logical to conclude that long COVID is a multisystem disorder entailing multiple mechanisms including viral invasion of the CNS, hypercoagulable states, and neurologic effects of the immune response [70].

The N and P affliction and morbidities in Long Covid

There is substantial evidence for neurological and psychiatric morbidity in the Long Covid patients. The retrospective cohort study by Taquet, et al. using data from the TriNetX electronic health records network, has highlighted the prevalence of various neurological and psychiatric sequelae in the post-COVID-19 patients [5]. The manifestations included ischaemic stroke and intracranial haemorrhage; nerve, nerve root, and plexus disorders; myoneural junction and muscle disease; encephalopathy; insomnia, mood and anxiety disorders, and substance use disorders; psychosis and dementia; and encephalitis, Parkinsonism and GBS. The estimates were affected by COVID-19 severity, ICU admission, and encephalopathy, and among 236 379 COVID-19 manifested one or more N and P manifestations. Compared with neurological disorders, common psychiatric disorders (mood and anxiety disorders) showed a weaker relationship with the markers of COVID-19 severity in terms of incidence. There is a significantly increased risk of N and P disorders, and N and sequelae of COVID-19 are widespread and may persist for and beyond 6 months (Figure 5).

Early in the pandemic, concerns were raised about the potential for serious and widespread neurological and psychiatric adverse outcomes following COVID-19 [1]. The psychiatric diagnosis was more common in patients with COVID-19 in the 14–90 days after SARS-CoV-2 infection than in those with several other acute illnesses [2]. A relationship between COVID-19 and ischaemic stroke has been well described, though COVID-19 seems to be a stronger risk factor for intracranial haemorrhage, albeit a rarer event, than for ischaemic stroke [3]. Data on a relationship with dementia have been sparse. The initial alarming reports of GBS in relation to COVID-19 do not seem to have been borne out by this or other large-scale epidemiological studies [4]. Similarly, concerns about a wave of encephalitis lethargica, analogous to that sometimes linked to the 1918 influenza pandemic, were not supported by the rather equivocal relationship between COVID-19 infection and parkinsonism, and the delayed neuropsychiatric sequelae such as post-encephalitic parkinsonism, do not occur after COVID-19 unless the delay exceeding one year.

The prolonged N and P manifestations in Long Covid

The patients with severe COVID-19 illness experience neurological complications such as delirium, cognitive difficulties including confusion and memory loss, which may persist for variable time after the acute symptoms have cleared. They may suffer with prolonged loss of smell and/or taste. One of the most insidious long-term effects of COVID-19 is severe fatigue manifesting as crippling exhaustion and malaise after having the virus. In a study of 143 COVID-19 patients discharged from a hospital in Rome, 53% reported fatigue and 43% had shortness of breath an average of 2 months after their symptoms started [43]. A study of patients in China showed that 25% had abnormal lung function after 3 months, and that 16% were still fatigued [71]. These symptoms resemble chronic fatigue syndrome, also known as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The ME/CFS patients suffer with wide-ranging and debilitating symptoms such as fatigue, unrefreshing sleep, cognitive difficulties, postural orthostatic tachycardia, and joint and muscle pains. In addition, the dysbalanced immune system caused by COVID-19, may lead to various autoimmune disorders manifesting as multi-system inflammatory syndrome due to inflamed vascular system, transverse myelitis and GBS, dysautonomia, disseminating encephalomyelitis, necrotizing haemorrhagic encephalopathy, cranial nerve palsies including facial nerve palsy, and Parkinson's disease-like symptoms which may persist.

Managing COVID-19 N and P manifestations

Investigations and Imaging for N & P Symptoms

Clinical and lab findings in patients with CNS symptoms: Patients with COVID-19 may develop delirium and

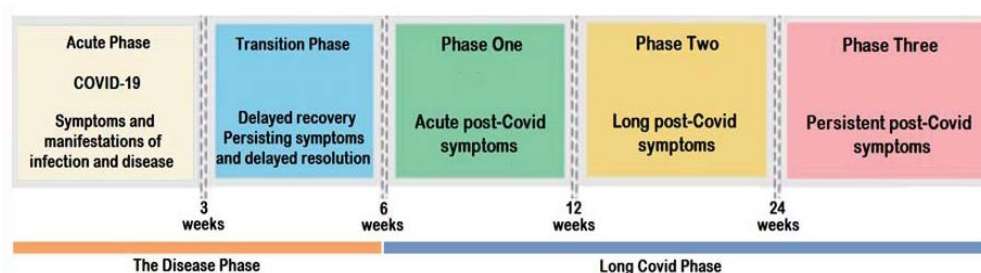


Figure 5: The timeline for neurological and psychiatric manifestations in COVID-19 and Long Covid.

agitation requiring sedation, whereas others manifest encephalopathy with somnolence and a decreased level of consciousness [42]. Corticospinal tract signs such as hyperreflexia, extensor plantar responses, are common, and seizures have been described along with encephalopathy in patients with COVID-19.

In general, the patients with CNS symptoms had lower lymphocyte levels, platelet counts, and higher blood urea nitrogen levels compared with those without CNS symptoms. For the severe subgroup too, patients with CNS symptoms also had lower lymphocyte levels and platelet counts and higher blood urea nitrogen levels compared with those without CNS symptoms. For the non-severe subgroup, there were no significant differences in laboratory findings of patients with and without CNS symptoms. Consistent with the previous studies, muscle symptoms were common and associated with higher creatine kinase and lactate dehydrogenase levels than those without muscle symptoms.

Most of the COVID-19 patients with encephalopathy typically have no evidence of brain inflammation on cerebrospinal fluid (CSF) analysis or neuroimaging studies. The case series reporting CSF analysis from COVID-19 patients have revealed no white cells and negative reverse transcription polymerase chain reaction (RT-PCR) assays for SARS-CoV-2 [8]. The findings on electroencephalography in COVID-19 patients are nonspecific. In a study involving 111 ICU patients the most frequent EEG finding was moderate generalized slowing (57%), and epileptiform findings were observed in 30% and seizures in 7% [72]. The patients who have elevated white blood cell count in CSF should undergo further evaluation for encephalitis and other conditions.

Neuroimaging findings in patients with CNS symptoms: The neuroimaging abnormalities have been described in patients with COVID-19-related encephalopathy are non-specific. Patterns of MRI abnormality include signal abnormality in the medial temporal lobe, multifocal white matter lesions visible on FLAIR and diffusion-weighted imaging with associated haemorrhage, and isolated white matter microhaemorrhages. The MRI may show ischemic stroke in patients with focal or lateralizing signs on examination, leptomeningeal enhancement, and findings suggestive of encephalitis. Cytotoxic lesions in the splenium of the corpus callosum have also been reported in adult patients with COVID-19-related encephalopathy as well as in a few children with multisystem inflammatory syndrome in COVID-19 [73,74].

Guidelines, therapeutics and rehabilitation measures

In general, the N and P manifestations in COVID-19 patients are variable and can emerge early or during the clinical course, or later as long-term complications. Further, presently our information about long-term N and P effects of COVID-19 and the medical, psychological and rehabilitation needs of these patients is limited [75]. In general, the N and P manifestations are to be dealt with in accordance with the symptomatic and standard therapy, for example, in patients of intracranial haemorrhage, an optimal blood pressure control is desirable; for raised intracranial pressure mannitol along with other decongesting measures, for seizures the anti-epileptic drugs, for patients with ischaemic stroke, anticoagulation may be recommended, and for GBS intravenous immunoglobulins may be helpful. The German Society of Neurology (DGN, Deutsche Gesellschaft für Neurologie), has come out with recommendations for guidance for the care of COVID-19 patients regarding neurological manifestations [76].

The Association of British Neurologists has also come out with guidelines to deal with the patients with various neurological diseases who are at an increased risk for COVID-19. The diseases with risk are divided into low, moderate, and high categories. Mild-to-moderate forms of common neurological diseases such as Parkinson's disease (PD), multiple sclerosis and epilepsy do not confer any increased risk as long as swallowing and breathing mechanisms are normal. Patients with advanced PD are at a high-risk for COVID-19 because of rigid respiratory muscle and impaired cough reflex. Further, as PD patients have reduced number of ACE-2 receptors on dopaminergic neurons, COVID-19 infection may worsen symptoms due to increased requirement of the dopaminergic drug, and the patients with advanced disease who on levodopa are vulnerable. Diseases causing weakness of bulbar and respiratory muscles are considered high-risk and include motor neuron disease, myasthenia gravis, myopathies and GBS. The risk-benefit ratio should be assessed and individualized for each patient [77].

Conclusion: evolving concepts and strategies

Overview: the disease tolerance approach

The present global COVID-19 pandemic has highlighted the need to understand that how we survive infections, rather than kill the infection [78]. It has been said that the COVID-19 pandemic may be different from the ways we often think about the treatment of infectious diseases. As understood, the successful response to COVID-19 requires a

multipronged approach, with the governments enforcing lockdowns and social distancing measures, the researchers and scientists working to identify a successful vaccine for the prevention of future infections and mortalities, and the potential COVID-19 treatments are being tested including antivirals and other compounds to inhibit viral replication, and its pathological fallouts.

As established, the antivirals are likely to be effective for some cases of mild COVID-19 by reducing the length of infection and reducing further transmission, but for the patients with severe and critical disease and who are destined for hospitalization and intensive care, the antiviral-based strategy may not work satisfactorily and the infection often progresses to severe and critical stages associated with pneumonia, ARDS and respiratory failure, and septic shock and multiorgan dysfunction. With the patients with severe disease the strategy available is to sustain physiological function by supportive measures such as ventilators and oxygen therapy, maintain fluids and circulation, and anticoagulating medications. Apart from developing antivirals, the research should be focused on drugs that promote physiological function during the infection. Such therapies are likely to promote survival and reduce the morbidity and mortality risk. This modality has been called the disease tolerance approach [79]. Further, for understanding to survive infection rather than kill an infection approach, infectious disease must be analyzed at the molecular, cellular, organ, physiological, and organismal levels.

The Cell therapy strategies and applications

SARS-CoV-2 initially emerged as causing pneumonia, ARDS, and respiratory failures. However, COVID-19, as the disease manifests, afflicts the immune, GI, cardiac, renal, and nervous systems, and among organs. For the subacute and chronic sequelae of COVID-19 including N and P manifestations, it is crucial to focus research efforts on finding therapies that can deal with the acute damage in a targeted manner and also restore physiological functions and tackle with the long-term consequence of the disease. The cell therapies have the potential to replenish the damaged tissue and organs and deal with the deranged immune system [80]. Overall data suggests that cell therapies may be applicable in particular pathogenetic aspects of COVID-19. Specific factors such as dosing of the cells, route of administration, allogenic versus autologous cells, role of immunosuppressive therapy, and tolerance of treatment should be considered and tailored to patient-specific manifestations.

The cellular tropism of SARS-CoV-2 is largely determined by the distribution of ACE2 receptors in various organs. The ACE2 is primarily expressed in the lungs, intestinal tract, heart and vasculature, and kidneys; with lower levels of expression in organs such as the brain, thyroid, adipose tissue, breast, male and female genital systems, and skeletal muscle. Many organs that express higher levels of ACE2 are not major sites of viral replication, indicating that expression of other host factors, including TMPRSS2, NRP1, and host restriction factors influence the viral tropism. Specific pathogenesis of COVID-19 in various organs, entails identification for potential cell therapy applications encompassing mesenchymal stromal cells (MSCs), induced pluripotent stem cells (iPSCs), T cells, and other targeted cell therapies for various organ systems. For the N and P manifestations, it may involve oligodendrocyte precursor cells and neural precursor cells to restore and regenerate depleted myelin sheath layer and damage due to ischemic strokes. Based on current understanding of the cellular and molecular mechanisms underlying remyelination, myelin and oligodendrocytes appear to be viable therapeutic targets to alleviate brain injury [81].

The research advances and evolving possibilities

There is a need to build on early advances in our understanding of SARS-CoV-2 and the disease to further identify and understand immediate and long-term consequences of disease and develop safe and effective therapeutic modalities and vaccines to control and prevent the current COVID-19 pandemic [82]. The future research perspectives and plans, and disease preventive and therapeutic modalities for COVID-19 should be structured on certain disease-related priorities, such as, continuing research related to SARS-CoV-2 biology, pathogenesis, emerging viral variants, and their impact on infection transmission.

Further, there is need to identify and test promising COVID-19 therapeutics, including the discovery and development of novel antivirals, including SARS-CoV-2-specific and broad-spectrum antivirals; virus-targeted antibody-based therapies including monoclonal and polyclonal antibody products, and host-directed strategies to treat COVID-19, such as immunomodulators. As regards the COVID-19 vaccines, we need to develop next-generation COVID-19 and pan-coronavirus vaccine candidates to provide broad and durable protection against SARS-CoV-2, and to upgrade variant-specific vaccine candidates and increase the durability of host immunity. Finally, we have to address the need to

characterize, prevent, and treat post-acute sequelae of SARS-CoV-2 infection (PASC), including the N and P manifestations to preserve and improve the quality of life.

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Chapter 6: Involvement of Kidneys and Endocrine System, and Skin in COVID-19 and Long Covid

Background

Renal, endocrinal and dermal disorders: COVID-19 is demonstrated to be a systemic disease with pulmonary and extrapulmonary manifestations which increase the severity and lethality of COVID-19. Kidney involvement in patients with COVID-19 is common and the reported rates of renal injury of are high and as per the available evidence affects over 20% of hospitalized patients and over 50% of intensive care unit (ICU) admitted patients. Similarly, endocrine involvement is present to variable extent in COVID-19 patients with moderate and severe disease. As regards dermatological involvement, its clinical spectrum is both heterogeneous and complex, and its link with severity of the disease is not clearly established. Albeit the assessment of the cutaneous manifestations of COVID-19 may enable early diagnosis or help in defining the overall prognosis.

The involvement of kidneys in COVID-19: The COVID-related nephropathy or acute kidney injury (AKI) is a potential complication impairing renal function and contributing to worsen the overall prognosis. SARS-CoV-2 infects the host through the ACE-2 receptors, which are expressed abundantly in the renal tissues. The kidney damage may occur both due to primary mechanisms directly related to the virus, and secondary mechanisms, linked to the hemodynamic and immune response to the virus. The renal abnormalities occur in the majority of patients with COVID-19 pneumonia. In addition, the co-existing chronic renal conditions, high blood pressure and diabetes increase the risk of kidney disease in COVID-19. The management of COVID-19 associated AKI includes supportive treatment, avoiding nephrotoxic drugs, and renal replacement therapy.

Endocrine affliction and manifestations: The endocrine organs, such as, pancreas, thyroid, testes, ovary, adrenal glands, and pituitary abundantly express ACE2, and therefore involved in SARS-CoV-2 infection. In turn, the endocrine disorders influence the functional abnormalities, the propensity, clinical course, and outcomes of COVID-19. Severe COVID-19 illness is more common in men, older age group and those with one or more co-morbidities, mostly of metabolic and cardiovascular nature. In fact, there is evolving a concept about an endocrine phenotype related to COVID-19. There is a high risk of morbidity and mortality in COVID-19 patients with diabetes, which can be decreased, but not completely abolished, by appropriate glycemic control. Apart from diabetes, obesity has been linked with high risk of prevalence and severity.

Dermatological involvement in COVID-19: There occur various specific as well as non-specific cutaneous manifestations in COVID-19, which have been increasingly reported in the recent studies. The incidence of the skin manifestations is variable and range from 0.2 to 20%. There have been reported morbilliform rash, pernio-like lesions, vesicular varicella-like eruptions, urticarial rash, retiform purpura and necrotic vascular lesions associated with COVID-19. The cutaneous manifestations range from benign to those associated with severe disease, though as such the association of certain skin manifestations with severity of COVID-19 is not established. There may occur recurrent COVID-19-associated pernio-like lesions. The skin manifestations in some COVID-19 patients may represent reactions to the drugs used.

Conclusion: prognosis and therapeutics: COVID-19 is a systemic disease with pulmonary and extrapulmonary manifestations, can affect almost every organ including the skin, and has variable severity and lethality. In addition, it is accompanied by various cardio-vascular, renal, gastrointestinal, and neurological complications. There being no specific treatment for COVID-19, the cornerstone of management of is symptomatic and supportive care. In those with AKI and deranged renal function RRT may be required, those with worsened diabetes or new onset hyperglycemia require monitored insulin treatment, and in those with glucocorticoid deficiency due to HPA axis or adrenal failure use of glucocorticoids is recommended. The dermatological lesions are mostly benign, resolve in due course, and treated symptomatically.

Renal, endocrinal and dermal disorders

The SARS-CoV-2 causing COVID-19, affects different people in different ways. In most cases the infection leads to mild to moderate illness, which recovers uneventfully without hospitalization. In the moderate to more severe cases, the clinical spectrum ranges from upper respiratory tract infection to pneumonia and ARDS. COVID-19 is demonstrated to

be a systemic disease with relevant extrapulmonary manifestations which increase the lethality of COVID-19 and mainly include vascular, cardiac, kidney, gastrointestinal, and central nervous system complications.

Kidney involvement in patients with COVID-19 is common, as opposed to initial reports considering AKI an infrequent occurrence, and ranges from the presence of proteinuria and haematuria to acute kidney injury (AKI) requiring renal replacement therapy (RRT). The reported rates of AKI are high and as per the available evidence affects over 20% of hospitalized patients and over 50% of the ICU admitted patients [1]. Despite considerable advances in understanding and management of other forms of AKI, relatively little is known about the pathogenesis or optimal management of COVID-19 associated AKI. Further, COVID-19-associated AKI is correlated with high mortality and is a major contributor for all-cause COVID-19 in-hospital mortality. The strategies about the prevention and management of COVID-19-related AKI are evolving and the impact of COVID-19 on long-term renal damage and dysfunction needs to be researched further [2].

Similarly, the endocrine involvement is present to variable extent in COVID-19 patients with moderate and severe disease. The involvement of the endocrine system is expected in COVID-19 as the interplay between SARS CoV-2 infection and the endocrine system occurs at multiple levels. The widespread presence of ACE-2 receptors on various endocrine tissues suggests the possibility for direct viral infection. In addition, the interactions via the activation of inflammatory mediators and indirect immune-mediated damage can occur leading to various endocrinopathies [3]. In COVID-19, functional hypopituitarism may occur by direct and indirect effects on the hypothalamo-pituitary axis resulting in inappropriate adrenal response to stress. The possible immune-mediated damage to thyroid glands may result in subacute thyroiditis. Various mechanisms demonstrate direct virus-induced beta cell apoptosis and immune-mediated beta-cell damage in COVID-19, precipitating hyperglycemia in known diabetics and uncovering insulin resistance in those previously undiagnosed.

As regards the dermatological involvement in COVID-19, there are several studies on incidence and manifestations of cutaneous lesions in outdoor and hospitalised patients. The clinical spectrum of cutaneous manifestations observed in COVID-19 patients is both heterogeneous and complex. However, the link between skin manifestations and the severity of the disease is not clearly established [4]. The skin manifestations associated with COVID-19 probably reflect the activation of pathogenic pathways by direct viral invasion, inflammatory response processes, vascular or systemic complications, or even treatments. The assessment of the cutaneous manifestations of COVID-19 may enable early diagnosis or help in defining the overall prognosis [5].

The involvement of kidneys in COVID-19

Incidence and prevalence of the nephropathy

The kidney injury or nephropathy is a potential complication of SARS-CoV-2 infection, which impairs the renal function and contributes to worsen the overall prognosis. The COVID-related nephropathy may manifest as AKI and is considered a marker of disease severity and an adverse prognostic factor for survival [1]. The incidence of AKI appears to vary in various studies, possibly due the population difference, disease severity, and AKI definition used in the particular study. The term, AKI has now replaced ARF, acute renal failure. AKI has been defined as an abrupt renal event which encompassing both renal structural damage and renal dysfunction. The AKI denotes as increased serum creatinine level (by 0.3 mg/dL within 48 h or > 1.5 times from its baseline level) or a decreased urine output (< 0.5 mL/kg/h for 6 h) according to the Kidney Disease Improving Global Outcomes guidelines [6]. It has been observed that those with severe AKI (stage III) may require renal replacement therapy (RRT), and have a higher mortality than those with stage I or II stage. Heart-kidney crosstalk could also contribute to AKI in COVID-19 patients [7]. Thus, viral cardiomyopathy and acute viral myocarditis can both contribute to renal vein congestion, hypotension and renal hypoperfusion, leading to a reduction in glomerular filtration rate. Patients with acute kidney insufficiency show a more severe disease course and may require admission in intensive care units. Particular attention should be paid to those with a prior kidney disease, such as chronic kidney disease, or renal transplant recipients.

AKI is an important complication of COVID-19, occurring in 0.5% - 7% of all cases and 2.9% - 23% of ICU patients [8]. A large Italian study involving over 2000 hospitalized patients with COVID-19 has reported the incidence of AKI about 27.8% [9]. A retrospective cohort study of 191 hospitalized COVID-19 patients in Wuhan noted that AKI occurred in 28 (15%) patients and was more frequent in critically ill patients [10]. Another retrospective Chinese study observed a high % age (75.4%) of patients with acute kidney injury among 333 hospitalized COVID-19 pneumonia patients [11].

The overall incidence of AKI ranges from 0.5% to 80.3%, although the study reporting the upper value considered only critically ill patients. In fact, the severity of pneumonia and ARDS have been identified as the most important risk factors for the development of kidney failure and subsequent poor function recovery [12]. It appears that, the initial reports from Wuhan suggested quite low prevalence of AKI in COVID-19 patients ranging from 3-9%, and subsequent studies have found a relatively high prevalence of AKI amounting to about 15% [13].

The AKI is more common among patients with more severe disease, particularly in those recovering in the ICU, and is considered a negative prognostic factor for survival. The clinical course for COVID-19 pneumonia patients developing renal dysfunction is unfavourable. Older age, hypertension and diabetes were associated with ARDS development, and subsequently AKI. In a retrospective study of 201 COVID-19 pneumonia patients, 41.8% developed ARDS and 4.5% developed AKI [14]. The mortality rate of COVID-19 patients with AKI is high and as observed by Cheng, et al. the in-hospital mortality was significantly higher in patients with proteinuria, haematuria, elevated creatinine and urea, and AKI stages 2 and 3 [15]. Further, patients with AKI had higher mortality compared to those without AKI, 35% and 16.3%, respectively [16]. In a notable study, the patients with COVID-19 pneumonia, who presented with kidney dysfunction had higher mortality rates than patients without kidney involvement, 11.2 and 1.2%, respectively [11]. In a large study involving 5,449 hospitalized patients, the incidence of AKI was 36.6 with 14.3% of patients requiring dialysis. Xiao, et al. have reported that most patients recover from AKI stage 1, but those who progress to AKI stage 2 or 3 have a high mortality rate [17].

The pathogenesis of renal injury in COVID-19

SARS-CoV-2 infects the host through the ACE-2 receptors, which are expressed abundantly in the renal tissues. The kidney damage may occur both due to primary mechanisms directly related to the virus, and secondary mechanisms, linked to the hemodynamic and immune response to the virus [18]. The SARS-CoV-2 infection via ACE2 may lead to local and systemic pathophysiological changes, including cellular immune disorder, cytokine storm, immune complex deposition, endothelial cell injury, thrombus formation, glucose and lipid metabolism disorder, and hypoxia, aggravating the renal injury. In addition, the severity of AKI is associated with factors such as older age, higher body mass index, hypertension, DM, and history of heart failure (Figure 1).

Mechanisms of direct renal damage: The virus, SARS-CoV-2 shows renal tropism and invasion and replication in renal parenchyma appears to play a role. SARS-CoV-2 binds to ACE2 through the S1 subunit, directly causing damage to intrinsic renal cells and clusters of virus-like particles (VLPs) are found in the renal tubular epithelium and podocytes. The virus could reach through blood circulation, bind to, and internalize with ACE2 receptors, invade, and replicate in kidney cells expressing the ACE2 receptor, including renal tubular epithelial cells, podocytes, and others. However, the viral load in the kidneys is low and unevenly distributed [19]. The virus can directly infect glomerular cells and renal tubules and the viral RNA has been detected as cytoplasmic inclusions and in urine of COVID-19 patients [20]. Further, the viral invasion and replication can induce tubular necrosis and lymphocyte infiltration. Further, viral infection can induce tubular damage through the deposition of the membrane attack complex (MAC) as the final step of the complement cascade on tubules and infiltration of CD68⁺ macrophages in the tubule-*interstitium*. These lesions may lead to microvascular dysfunction, tissue inflammation, coagulopathy, and endotheliitis.

The kidneys, as an organ are profoundly affected by SARS-CoV-2 infection. There is involvement of renal parenchyma

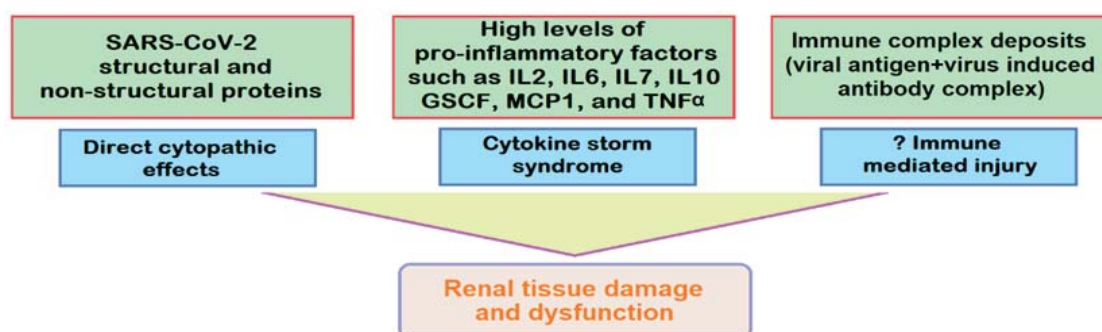


Figure 1: The mechanisms of direct and immune-related damage in COVID-19-related nephropathy.

and interstitium leading to AKI. There is diffuse acute proximal tubular injury with loss of brush border with nonisometric vacuolation and various casts are seen in the tubular lumen. The glomerular lesions are minor, with varying degrees of morphologic changes and ischemic glomeruli. Distal tubules and collecting ducts are affected less and show occasional cellular swelling and interstitial space oedema without significant inflammation. The endothelial injury includes cellular swelling, subendothelial expansion, and endothelial proliferation with deposits of IgG, IgA, IgM, and C3. In severe injury, segmental microthrombi are seen in glomerular capillary loops with podocyte vacuolation and detachment from the glomerular basement membrane.

The histopathological analysis renal samples from autopsies of COVID-19 patients showed acute tubular necrosis (ATN) ranging from moderate to severe ATN. Diffuse proximal tubule injury was evidenced as the loss of brush border, vacuolar degeneration, dilatation of the tubular lumen, detachment of epithelium, and frank necrosis (Figure 2). In addition, the distal tubules and collecting ducts showed nonspecific cellular swelling and interstitial infiltrates [21].

Another study, involving post-mortem analysis of 42 patients from the USA also confirmed ATN being the predominant finding with presence of focal fibrin thrombi [22]. There was seen endotheliitis of glomerular capillaries and SARS-CoV-2 nucleocapsid protein (NP) was detected in renal tubular cells [23].

Mechanisms of indirect renal damage: Added to the direct cytopathic effect, there is another aspect of ACE2 involvement by the virus. While ACE converts angiotensin I (Ang I) to angiotensin II (Ang II), ACE2 degrades Ang II to angiotensin 1–7 (Ang 1–7). Ang II plays a role in vasoconstriction and adrenergic stimulation, while Ang-(1–7) opposes the Ang II-AT1 axis through vasodilatation, and anti-inflammatory and anti-fibrotic action, mainly through increasing nitric oxide production. The RAS plays a key role in maintaining blood pressure homeostasis and water-electrolyte balance. By degrading Ang II into Ang (1–7), ACE2 negatively regulates the activated RAS, and shows protective effects, including vasodilation, as well as suppression of inflammation, oxidative stress, and cell apoptosis. During SARS-CoV-2 infection, following binding to SARS-CoV-2 S protein, the external domain of ACE2 is cleaved, and the transmembrane domain is internalized, leading to downregulation of ACE2 and relative increase in ACE activity leading to overproduction of Ang II, resulting in a proinflammatory state, decreased vasodilatation and deterioration of renal function [24]. The pre-existing CKD patients, especially those with diabetic nephropathy, already have existing upregulation of ACE and downregulation of ACE2, and thus high risk of adverse outcomes.

Apart from this, the indirect renal damage may occur due to pro-inflammatory cytokines, systemic effects of the disease, and organs crosstalk entailing renal dysfunction and damage due to pulmonary, cardiovascular, GI, and other organ involvements in COVID-19 [18]. Moreover, these mechanisms are intricately interconnected. The kidney injury may occur due to renal hypo-perfusion as result of humoral response to virus infection, hemodynamic and haemostatic factors including micro-angiopathy and thrombosis, erratic and hyper-immune response, and activation of the complement system. The excessive activation of the complement, similarly to CSS, may cause endothelial injury and the activation of the coagulation cascade. In addition, systemic hypotension, as a result of severe dehydration, low cardiac output, or septicemic vasodilatation, may compromise the renal blood flow. Further, the alveolar-capillary leakage and renal vein congestion may worsen it.

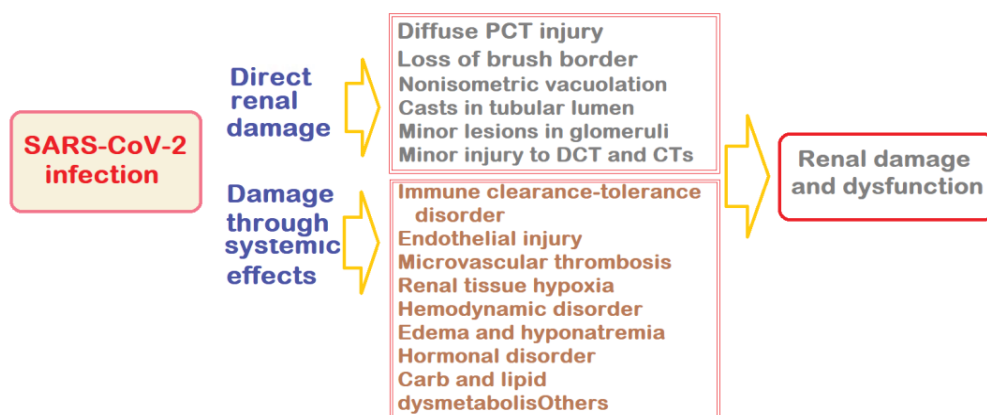


Figure 2: The histopathological changes due to direct and indirect mechanisms in COVID-19-nephropathy.

In the severe SARS-CoV-2 infection a precipitous secretion of pro-inflammatory cytokines leads to cytokine release syndrome (CRS) or cytokine storm syndrome (CSS), which is a harbinger of systemic inflammatory response syndrome (SIRS) responsible for tissue damage in various organs and multiple organ dysfunction syndrome - MODS [25]. It is also responsible for endothelial dysfunction and a pro-thrombotic milieu leading to small vessel vasculitis and micro-vascular thrombosis, a condition named thrombotic microangiopathy (TMA). There may occur AKI as a fallout of renal damage mediated by inflammation, endothelial dysfunction, and micro-vascular thrombosis. The pro-inflammatory Interleukin-6 (IL-6) appears to play a central role in CRS [26]. The indirect renal injury may occur due to CSS causing collapsing focal segmental glomerulosclerosis. Simultaneously, CSS, hemodynamic instability, rhabdomyolysis, sepsis, and hypoxia can potentially cause renal damage [27].

The renal damage leading to AKI and renal dysfunction can occur along with involvement of other organs, such as lungs, heart, and GI organs. The phenomenon has been described as organ crosstalk. Thus, in patients with CSS, AKI may occur as a result of intrarenal inflammation, increased vascular permeability, volume depletion and cardiomyopathy. There occurs systemic endothelial injury manifesting clinically as pleural effusions, ascites, oedema, intravascular fluid depletion and hypotension. Cytokine overproduction and IL-6 are involved in the alveolar and tubular damage through the bidirectional link, the lung-kidney axis in ARDS. Among patients with COVID-19, ARDS may cause renal medullary hypoxia and tubular cell damage, demonstrating the close relationship between the lungs and kidneys [7]. In addition, AKI is a part of multiple organ dysfunctions in septicaemia in COVID-19, which is complicated by systemic hypotension, renal hypo-perfusion, endothelial dysfunction, tubular cell damage, and inflammatory cells infiltration [16].

The course and outcomes of AKI in COVID-19

In general, the severity of SARS-COV-2 infection depends on the balance between clearance of the virus and tolerance of the human immune system. The activation of the IFN-1 signaling pathway can lead to the production of an autoreactive adaptive immune response. In addition, the host's anti-infection immune intolerance directly results in an overactive immune response and cytokine storm, resulting in tissue damage in various organs including kidneys. Apart from pulmonary involvement, AKI is one of the most frequent and complication in COVID-19. In the course of severe COVID-19, the renal dysfunction and acute renal insufficiency often occur in patients with healthy kidneys, characterized histologically by diffuse acute tubule damage. But COVID-19 is neither associated with acute T-cell mediated interstitial nephritis nor a specific glomerulonephritis [28]. The renal injury in COVID-19 patients usually manifests as increased serum creatinine, variable degrees of proteinuria and haematuria, decreased lymphocytes and increased inflammation markers, and radiographic abnormalities of the kidneys, showing the CT value of the kidney parenchyma lower than normal, indicating renal inflammation and edema [29].

AKI is more common among patients with more severe disease, particularly in those recovering in the ICU, and is considered a negative prognostic factor for survival [16]. Whereas during a median duration of 12 days of follow-up, nearly half of patients with AKI recovered, adverse short-term outcomes of renal involvement were associated with severity of COVID-19 pneumonia and COVID-19 patients with renal involvement had higher overall mortality (11.2%) compared with those without renal involvement having 1.2% [11]. The renal abnormalities, thus, occur in the majority of patients with COVID-19 pneumonia and severity of pneumonia is an independent negative prognostic indicator for renal complications (Figure 3). In addition, the co-existing chronic renal conditions, high blood pressure and diabetes increase

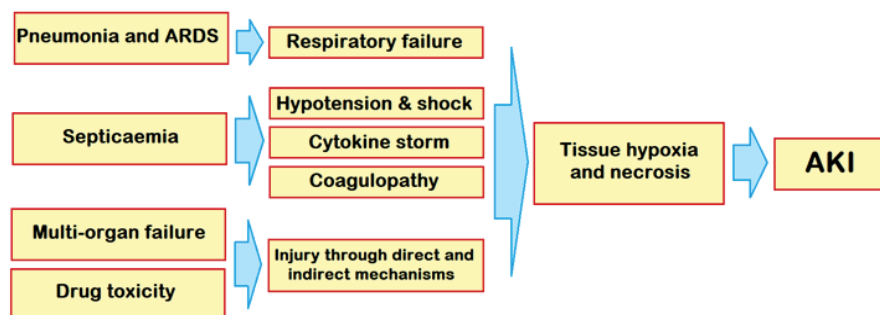


Figure 3: The pneumonia-ARDS link in COVID-19. Various factors like cytokine crisis, septicaemia, coagulopathy, and multi-organ dysfunctions play a role in development of renal tissue hypoxia and necrosis leading to renal damage and dysfunction. The drug toxicity is an important factor for development of renal tissue hypoxia and necrosis, and requirement of RRT.

the risk of renal involvement in COVID-19. Still, though, the SARS-CoV-2 related nephropathy and its fallout in patient with underlying kidney disease is not well-characterized, the findings indicate that although early renal abnormalities often resolve in such patients, intensive support, and careful monitoring of severe or critical illness is required for those with COVID-19 pneumonia with renal complications [30].

The renal involvement in COVID-19 has become an increasingly serious dilemma over time, as it may increase the risk of severe disease and mortality in COVID-19 patients. A recent study by Feng, et al. has revealed the dynamics of renal involvement superimposed on COVID-19 in relation to time and space [31]. The study provides a comprehensive overview of the spatiotemporal trend of renal involvement in COVID-19. The prevalence of AKI in the 30 studies included varied from 0.3% to 68.8% and the pooled probability of occurrence of AKI was 19%. Further, the study indicated that the pooled risk of AKI in Asia was 10%, as compared to outside Asia as being 35%. A surprising finding from this study was that the risk of AKI in patients with COVID-19 showing an upward trend over time. Thus, the COVID-19 patients enrolled after 1 March 2020 had a higher risk of renal involvement than those enrolled before March 1, 2020. The mutation of SARS-CoV-2, especially D614G mutation might have played a role in this finding. The pooled requirement for RRT was documented to be 7%, with the observation that the non-severe COVID-19 patients had a significantly lower need of RRT than severe COVID-19 patients, and RRT was less frequently required in COVID-19 survivors when compared to non-survivors.

In conclusion, compared with those who had non-severe COVID-19, the patients with severe COVID-19 had a significantly higher risk of developing AKI and COVID non-survivors showed a statistically significant higher risk of developing AKI when compared to survivors. Simultaneously, as shown in another study, the pre-existing CKD patients on RRT appears to be associated with a significantly high risk of severe COVID-19 infection and mortality [32]. The SARS-CoV-2 infected kidney patients show high overall mortality, 27.9% of infected dialysis patients and 6% of kidney transplant patients with COVID 19 infection died, according to this registry. In addition, SARS-CoV-2 RNA has been detected in renal tissue in the autopsy studies in over 60% of patients. Retrospectively, this finding was associated with higher age, a higher number of comorbidities, and a diminished patient survival [33]. Due to the hypercoagulability state associated with COVID-19, systemic anticoagulation is advised [34]. The current management of COVID-19 associated AKI includes supportive treatment, avoiding nephrotoxic drugs, and an early start of renal replacement therapy.

Endocrine involvement and manifestations

The endocrinopathies and potential COVID-19 risk

Severe COVID-19 illness is more common in men, further suggesting that sex and possibly male and female sex hormones, affect the prevalence of the infection. Further, the patients affected by severe COVID-19 are older and have one or more co-morbidities, mostly of metabolic and cardiovascular nature, compared to those suffering with mild or non-severe disease [35]. The most frequent phenotype of a COVID-19 patient requiring hospitalization is, thus, an elderly (60+ age group) male with co-morbidities such as hypertension, diabetes mellitus, obesity, coronary heart diseases, and cerebrovascular disease [36]. This metabolic phenotype is relatively consistent across European countries and the USA, while in Chinese studies this phenotype is less frequently observed, and age is lower [37].

Most of endocrine organs, namely pancreas, thyroid, testis, ovary, adrenal glands, and pituitary, express ACE2, and therefore involved in the SARS-CoV-2 infection [3]. More recently the use of glucocorticoids has shown promise as a treatment in moderately to severely ill COVID-19 patients. In addition, COVID-19 disproportionately affects persons with endocrine disorders, conditions, who carry an increased risk of morbidity and mortality [38]. Thus, as well known, the patients with endocrinopathies such as diabetes mellitus (DM), hypertension (HTN), obesity and metabolic syndrome are at higher risk for COVID-19 related complications [10]. The studies from the UK and US have also indicated a high prevalence of DM and obesity in COVID-19 non-survivors and severe cases [39]. In a study from the US, commonly reported cardiometabolic comorbidities associated with COVID-19 were HTN -49.7%, obesity 48.3%, DM 28.3%, and cardiovascular disease 27.8% [40]. In background of similar other studies, both the WHO and the US Centers for Disease Control and Prevention (CDC) list DM, HTN, and obesity as risk factors for development of more severe COVID-19 outcomes [41].

Interplay between endocrinopathies and COVID-19

The human endocrine system is evidently involved in SARS-Cov-2 infection and the endocrine functional abnormalities commonly occur. In turn, the endocrine disorders influence the functional abnormalities the propensity, clinical course,

and outcomes of COVID-19. Pathophysiologically, ubiquitous expression of ACE2 is responsible for the entry of SARS-CoV-2 at the cellular level, accompanying endothelial damage, and altered immune response contributing to the multi-organ involvement in COVID-19. The resultant elements such as viral cytopathic effect, endothelial damage, hypoxaemia, and altered and erratic immune response directly or indirectly affected and negatively influence the endocrine functions. In fact, there is evolving a concept about an endocrine phenotype related to various endocrine organs and COVID-19 [42]. Moreover, other endocrine and metabolic diseases such as obesity, hypovitaminosis D, and adrenal dysfunctions may have an impact on susceptibility and severity of COVID-19 (Figure 4).

There are certain adverse factors related to immune dysregulation, which are increased in obesity, DM and HTN and may account for the severity of disease. The IL-6 level is significantly raised in DM, both type 1 and 2, and proportionately to BMI in obesity. IL-6 has a bidirectional relationship with DM as it is implicated in insulin resistance and disturbed glucose homeostasis. Further, the T-cells in type 1 DM are more sensitive to IL-6, leading to immune dysregulation and CRS. In HTN also, IL-6 levels are raised due to increased levels of angiotensin II and aldosterone, which trigger IL-6 secretion by the endothelium. The elevation of CRP is a downstream effect of IL-6, which is thus elevated in DM, HTN, and obesity. The DPP-4, another factor with independent pro-inflammatory effects, is also raised in DM and obesity. Taken together, these disruptors of immune regulation linked with pathophysiology of COVID-19 are prevalent in DM, HTN, and obesity, and may account for increased severity of the disease [43].

Pathophysiology and outcomes for COVID-19 in DM

The prevalence and outcomes for COVID-19 in DM: DM is a major risk factor for severe COVID-19 and a predictor of adverse outcome and mortality. Iacobellis, et al. reported that admission hyperglycemia was the best predictor of SARS CoV-2 radiological findings [44]. The inflammatory milieu and elevated cytokines in diabetes may in addition, contribute to severe disease, ARDS and multi-organs involvement. In turn, COVID-19 lead to worsening of insulin resistance in patients with pre-existing T2DM. Moreover, COVID-19 is often associated with hypokalaemia, which can worsen glucose control in patients with pre-existing T1DM and T2DM [45]. The hyperglycaemia or new-onset diabetes is an important predictor of worse outcomes in COVID-19, Whereas pre-existing DM is associated with severe disease, ARDS, and increased mortality. There is, thus, a bidirectional relationship between DM and COVID-19, both in terms of worsening existing conditions and new onset of diabetes.

The data on COVID-19 diabetic patients requiring hospitalization are variable among studies from different world regions. A large study involving 118,150 COVID-19 patients, which documented a prevalence of diabetes as 9.3%, documented that about 14.8% diabetic patients required hospitalization [46]. Whereas this data was 7.3% in China, 17.9% in South Korea and 43.3% in US veterans [47,48]. In a large UK cohort of people dying of COVID-19 in the hospital, 32% had T2DM and 1.5% had T1DM, and among people with diabetes, male sex, older age, renal impairment, non-white ethnicity, socioeconomic deprivation, previous stroke, and heart failure were associated with higher COVID-19-related mortality [49]. In addition, diabetes was also associated with longer hospital stay and the necessity of assisted ventilation

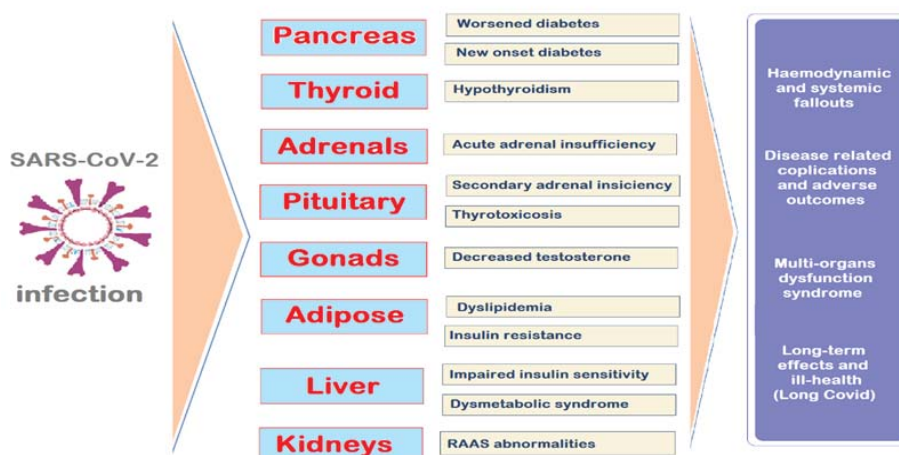


Figure 4: The multiple endocrinopathies in COVID-19, the hormonal abnormalities, and their fallouts.

and ICU admittance [50]. The recent data indicate that not only current glycemic control is related to outcomes, but prior metabolic control is also related to mortality in SARS-CoV-2 diabetic patients [51].

The etiopathophysiology and prognostic correlates: The expression of ACE2, the receptor for SARS-CoV-2 is abundant in pancreatic endocrine tissue, compared with the exocrine tissue. Thus, SARS-CoV-2 may directly damage pancreatic islets to acute insulin dependent diabetes mellitus but not acute pancreatitis [52]. In addition, SARS-CoV-2 might cause a bystander β -cell death via release of inflammatory mediators such as tumor-necrosis factor- α (TNF α) and interferon- γ . A systemic pro-inflammatory milieu, as evident by high amounts of interleukin-1 β , monocyte chemoattractant protein-1 (MCP-1) and inducible protein-10 even in patients with mild COVID-19 might play an additional role to accentuate the process of pancreatic islets damage. This has been supported by the autopsy findings. Wang, et al. found pancreatic injury in 17% of 52 COVID-19 patients with elevated serum amylase or lipase levels and two-third had abnormal blood glucose levels [53].

Various studies highlight the high risk with DM patients for COVID-19 [63]. In fact, during the clinical course of SARS-CoV-2 infection, patients with diabetes may present with milder symptoms initially, but they are at higher risk of rapid progression to severe pneumonia, ARDS, uncontrolled cytokine storm and hypercoagulable state contributing to an adverse prognosis (Figure 5). It has been hypothesized that SARS-CoV-2 infection in patients with diabetes may trigger physiological stress leading to increased secretion of hyperglycaemic hormones, such as glucocorticoid and catecholamines, resulting in exaggerated hyperglycaemia and diabetic complications, which in turn increase mortality and morbidity [54]. In this context, new-onset DM in COVID-19 patients, previously nondiabetic, has been consistently documented in several studies [55].

In fact, there are certain factors related to DM, which aggravate the risk for severe COVID-19 for several reasons [56]. First, DM may facilitate cell entry of SARS-CoV-2 by augmenting the surface expression of ACE2 through hyperinsulinemia-mediated reduction in ADAM metalloproteinase with thrombospondin type 1 motif 17 (ADAMTS17) activity [57]. ADAMTS17 is a member of the large ADAMTS family of zinc-dependent proteases, hence the role of zinc supplementation in COVID-19. Second, ACE2 modulators such as ACE1 inhibitors (ACEi), angiotensin receptor blockers (ARBs), and thiazolidinediones, which are used frequently in DM may upregulate ACE2 expression [58]. Third, DM is associated with complement system defects and dysregulated release of IL-6, IL-8 and TNF- α . The serum levels of inflammation-related biomarkers (interleukin-6, serum ferritin, C-reactive protein) and coagulation parameter (D-dimer) are high in COVID-19 patients with DM, and the molecular interplay between hyperglycaemia and various inflammatory markers leads to T-reg dysfunction and altered immune response [59]. Fourth, co-existing HTN and obesity, acting via HIF-1 α and toll-like receptors, may contribute to the pre-existing chronic inflammation leading to impaired immune-mediated clearance of SARS-CoV-2. Fifth, dipeptidyl peptidase-4 (DPP-4), a surface glycoprotein, which degrades glucagon like peptide 1 ('GLP-1', an incretin hormone), is known to be elevated in DM and obesity and has a pro-inflammatory effect [60]. And finally, as hyperglycemia is seen in 35% - 58% of inpatients with COVID-19 suggesting the burden of impaired glucose metabolism, the glucocorticoid use in COVID-19 patients should be selective, as it may also adversely affect the prognostic correlates for the favourable outcomes.

Therapeutic guidelines for COVID-19 DM patients: The increased risk of morbidity and mortality in COVID-19 patients with diabetes can be decreased, although not completely abolished, by appropriate glycemic control [42]. Because of the need for flexible dosing, insulin is the safest drug for the management of hyperglycemia in COVID-19 diabetic patients. Additionally, insulin has an anti-inflammatory effect. Higher dose of insulin may be required in patients on the glucocorticoid therapy. The DPP-4 inhibitors and GLP-1 receptor analogues are helpful, apart from having



Figure 5: The pathophysiology of pancreatic damage, cytokine storm syndrome, dysmetabolic effects, and coagulopathy-microangiopathy in COVID-19 diabetic patients influencing the disease course and outcomes.

immunomodulatory effects, they are lung-protective and may attenuate the chronic inflammatory state in DM. The patients under on hypoglycaemic agents will also need frequent glycemic monitoring and modifications in doses. The recent data indicate that treatment with metformin is associated with lower disease severity and mortality [61]. Thus, if there are no contraindications, the oral compounds may be continued. An Italian retrospective study has indicated that the use of sitagliptin was associated to a reduced mortality during hospitalization [62].

Obesity – the links and outcomes for COVID-19

Obesity is associated with increased susceptibility to SARS-CoV-2 infection, severe COVID-19 illness, and potential risk for adverse outcomes. With higher amount of adipose tissue there is increased expression of ACE2, which may increase the susceptibility to SARS-CoV-2 infection [63]. Obesity is associated with chronic adipose tissue hypoxia and there exists a state of chronic inflammation. As in DM, obesity is accompanied by increased levels of pro-inflammatory cytokines such as IL-1, IL-6, MCP-1, and TNF- α , produced by visceral and subcutaneous adipose tissue [64]. The obesity is linearly associated with raised C-reactive protein (CRP) levels, which is proximately triggered by adipocytic derived IL-6. In addition, higher levels of pro-inflammatory DPP-4 levels seen in obesity and the consequent hyperinsulinemia may both independently exacerbate COVID-19 risks. There exists concurrent immunological dysfunction predisposing to an exaggerated cytokine response, manifesting as severe disease and ARDS [65]. In addition, obesity is independently associated with coagulopathy and thrombosis risk and an increased predilection for microangiopathy and venous thrombosis.

In fact, obesity has been reported as the third most common comorbidity after DM and hypertension, and associated with high mortality, with a prevalence of 28% in COVID-19 non-survivors [66]. Further, the CDC has reported obesity being present in 48.3% of all COVID-19 hospitalized patients in the US [40]. A metaanalysis of clinical studies, comprising of a total of 6,271 patients showed that obesity was prevalent in 35.8% - 48.3% of hospitalized COVID-19 patients [67]. Obesity has been noted an independent risk for COVID-19 hospitalization in younger patients [68]. The National Health Service in the UK has also found obesity as a risk factor for severe disease and mortality in COVID-19 [39]. In light of various studies, the CDC updated its guidelines to include a BMI > 40 kg/m² as a risk factor for severe COVID-19 [41].

Thyroid involvement in COVID-19

There are studies to suggest that thyroid gland and the hypothalamo–pituitary–thyroid (HPT) axis, are affected in COVID-19, though there have not been found abnormalities in the thyroid follicular morphology apart from lymphocytic infiltration in the interstitium [69]. Thyroid dysfunction in COVID -19 may result from direct destruction of the gland by the SARS-CoV-2 virus, though tissue immunohistochemistry and PCR analyses have failed to detect SARS-CoV-2 in the thyroid gland despite expression of ACE2, precipitation of immune-mediated mechanisms, and sick euthyroid syndrome. A study of SARS-CoV-2 patients noted that TSH and free T3 concentrations were significantly lower in deceased patients than in recovered patients, with the difference in the T4 levels not being statistically significant [70]. The alterations in thyroid hormone levels may persist after clinical recovery.

The studies related to SARS-CoV are helpful in understanding the thyroid-related abnormalities in COVID-19 [71]. A study by Wang *et al* reported that serum levels of T3 and T4 in SARS-CoV patients were significantly lower than those in the control group, and low T3 levels correlated with disease severity. There was noted low levels of TSH in these patients suggesting HPT axis dysfunction [72]. Several cases of atypical subacute thyroiditis have been reported in COVID-19 [73]. Subacute thyroiditis related to COVID-19 is usually painless and may present with thyrotoxicosis, which may be followed by hypothyroidism. Patients are reportedly negative for thyroid antibodies [74]. In addition, autoimmune thyroiditis can occasionally be triggered by the cytokine storm in SARS-CoV-2 infection [75]. The studies suggest for the monitoring of thyroid function tests during acute illness as well as during convalescence from COVID-19 with the prospect of replacement therapy if required.

Gonadal hormones and COVID-19 susceptibility

Epidemiologically the susceptibility to SARS-CoV-2 infection in men and women is similar. But the sex-based differences and regulation of ACE2 in various organs may be responsible for dissimilar clinical manifestations in men and women [76]. However, the propensity for severe COVID-19 and hence mortality is higher in men compared to women [77]. Physiological mechanisms that are likely to play a role in sexual dimorphism of COVID-19 outcome include may include the differences in viral invasion as well as an inherent impact of related biological factors on the immune response against SARS-CoV-2 infection [78].

Pathophysiologically, there is an abundant ACE2 expression in the Leydig cells, Sertoli cells and the spermatogonia of the testes. It has been shown that androgens secretion might regulate transcription of the host entry factors of SARS-CoV-2 as well as immune response [79]. Thus, the significantly higher serum T:LH ratio in COVID-19 patients is positively associated with disease severity [80]. Whereas relatively elevated serum LH in men with COVID-19 negates the possibility of suppression of the hypothalamic-pituitary-testicular axis and hints toward primary Leydig cell damage leading to higher serum T:LH ratio and propensity to severe disease [81].

The Hypothalamic-pituitary-adrenal axis

The hypothalamic and pituitary tissues in brain express ACE2 and therefore may be involved in the viral infection. There can thus occur hypophysitis or hypothalamic damage directly or via immune-mediated, leading to a state of hypothalamo-pituitary dysfunction. The central hypocortisolism may occur in COVID-19 survivors, especially those complaining of unexplained fatigue, lassitude, malaise, and orthostatic syndrome. The patients with pituitary-hypothalamic disorders often have underlying diabetes insipidus, which may worsen leading to insensible water loss and hypernatremia. In the advanced phase of SARS-CoV-2 infection, central hypoadrenalism may occur due to blunting of the hypothalamic-pituitary-adrenal axis activation leading to glucocorticoid insufficiency in the critical illness setting [42]. The resultant adrenal insufficiency may lead to impaired immune response with neutrophil and natural killer-cell dysfunction [82].

In fact, the patients with severe COVID-19 may be more prone to develop critical illness-related corticosteroid insufficiency (CIRCI). These findings indicate the need for actively monitoring biochemical parameters like serum cortisol and ACTH. Symptomatic patients with orthostatic hypotension may require physiological doses of hydrocortisone replacement until HPA axis recovery. In fact, patients with adrenal insufficiency and Cushing's syndrome are at increased risk of SARS-CoV-2 infection. In addition, it is likely that cortisol dynamics may also be altered in patients with SARS-CoV-2 as ACE2 expression has been reported in the adrenal cortical cells. Further, the patients with adrenal deficiency states may be at increased risk of SARS-CoV-2 infection due to impaired immunity and neutrophil dysfunction. Furthermore, the patients with adrenal insufficiency, are at a higher risk of adrenal crisis after the infection. It must be added that the corticosteroid treatment in severe COVID-19 is presumptive and not associated with virus clearance, length of hospital stays, or duration of symptoms [83].

Dermatological involvement in COVID-19

Incidence and prevalence of dermal manifestations

There occur various specific as well as non-specific cutaneous manifestations in COVID-19 [84,85]. There is, in fact, a need to collate the cases and define the cutaneous manifestations of COVID-19 [86]. The COVID-19-associated cutaneous manifestations have been increasingly reported in the last few months [87].

The incidence of the manifestations is variable and range from 0.2% to 20.4% [47]. One study in Lombardy, Italy found that 20% of COVID-19 patients had some kind of skin manifestations. Another study of 181 COVID-19 patients found that 31% suffered from dermal micro-vascular complications [88]. In addition, the association of certain skin manifestations with the severity of the disease is not clear [89]. Further, the observed skin manifestations in some patients may represent cutaneous reactions to the drugs used for treatment in COVID-19 [90].

Types of dermatological manifestations in COVID-19

Among 171 laboratory-confirmed COVID-19 patients with cutaneous manifestations from the registry, the most commonly reported were morbilliform rash - 22%, pernio-like acral lesions - 18%, urticaria - 16%, macular erythema - 13%, vesicular eruption - 11%, papulosquamous eruption - 9.9%, and retiform purpura - 6.4% [91]. Other studies have reported similar finding with a varying rate of skin manifestations and there have been described six major types of skin manifestations associated with SARS-CoV-2 infection depending on clinical and histopathologic characteristics [92].

In an Italian study of 148 COVID-19 positive hospitalized patients were examined for cutaneous involvement. Analyzing history of recent drug intake, 60 patients were excluded that had used any new medicine in the 15 previous days. In the rest - 88 patients, 18 patients (20.4%) developed cutaneous manifestations, 14 patients had erythematous rash, 3 patients had generalized urticaria, and 1 presented with chickenpox-like vesicles. Trunk was the mainly involved region. Itching was low or absent and usually lesions healed in few days. There was not found any correlation with disease's severity [84].

The commonly observed skin manifestations are (Figure 6).

Exanthematous (morbilliform) rash – In several cases, a morbilliform rash predominantly on trunk is the most common cutaneous manifestation of COVID-19 [93]. It can also occur buttocks, popliteal pits, proximal anterior thighs, and lower abdomen, and rarely in crural folds, face, palmoplantar skin, and mucosa. The rash occurs either at the disease onset or, more frequently after hospital discharge or later during recovery. The usual histopathological findings are superficial perivascular lymphocytic infiltrate with abundant extravasation of red cells and focal papillary edema, in combination with dilated vessels in the upper and middle dermis, with no signs of thrombotic vasculopathy. The epidermis may show focal parakeratosis and dyskeratotic cells [94].

Pernio (chilblain)-like acral lesions – Pernio or chilblain-like lesions, called COVID toes, present as erythematous-violaceous or purpuric macules on fingers, elbows, toes, and the lateral aspect of the feet with or without edema and pruritus [95]. These lesions have been encountered in confirmed or suspected COVID-19 patients of all age groups, often late in absence of cold exposure or underlying conditions associated with pernio [96]. They appear as sudden painful, burning and itching red or purple discolouring of toes and fingers, and may be due to micro-thrombi secondary to virus-induced endothelial damage. The lesions usually resolve within 2 to 8 weeks, though a prolonged course of more than 60 days has been reported in some Long Covid patients [97].

The histopathology of the lesions shows mainly epidermal basal layer vacuolation, papillary dermis edema and erythrocyte extravasation, a perivascular and peri-eccrine dermal lymphocytic infiltrate, and mucin deposits in the dermis and hypodermis [98]. Dermal vessel thrombi are sometimes present. The pathogenesis of the dermatological lesions is not established, though it appears to be a primarily inflammatory process with histopathologic and direct immunofluorescence findings similar to those seen in idiopathic and autoimmune-related pernio [99].

Livedo reticularis-like vascular lesions – These vascular lesions have been encountered in a few patients with COVID-19, and usually occur as blotchy redness network-like rash on thighs and legs. In a series of 171 RT-PCR confirmed cases, these vascular lesions were noted in 5.3 and 2.3% of patients, respectively [91].

Livedo retiform necrotic vascular lesions – The retiform purpura and necrotic vascular lesions, occur on trunk or acral surfaces, and are associated with severe COVID-19. The pathogenesis may be complement-mediated microvascular injury and thrombotic vasculopathy, with an underlying hypercoagulation state and disseminated intravascular coagulation, suggested by increased levels of D-dimer, fibrinogen and fibrinogen degradation products, and a prolonged prothrombin time. The patients present with acro-cyanosis of the fingers and toes, skin blisters, and dry gangrene. The histology of skin lesions shows degeneration of dermal collagen, dermal edema, mucin deposits, and the presence of microthrombi in the dermal vessels.

Urticarial rash – A number of COVID-19 patients present itchy urticarial rash with or without concomitant fever affecting various skin locations. The urticarial rash can be localized or generalized and has been considered a diagnostic clue in early phase of infection [100]. Generally, it is associated with more severe COVID-19 infection. But being nonspecific, it can also be caused by drugs, medication, heat, cold, and pressure on skin.

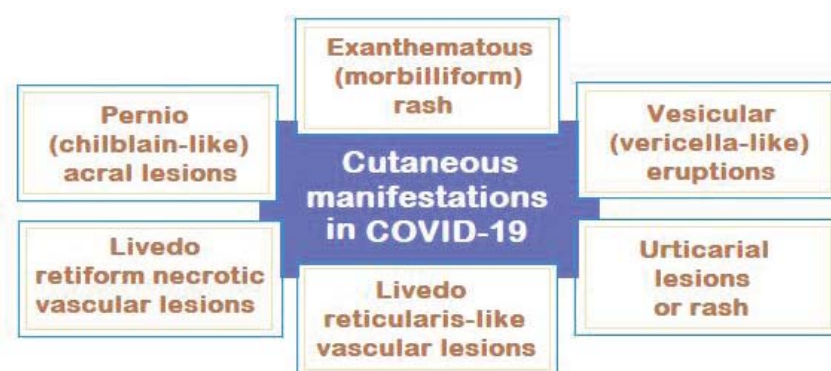


Figure 6: Cutaneous manifestations in COVID-19.

Vesicular (varicella-like) eruptions – There may occur vesicular-pustular, varicella-like, small monomorphic blisters associated with SARS-CoV-2 infection. They are often an early presentation and may have a haemorrhagic component [101]. These eruptions are located mainly on the trunk, particularly present in middle-aged COVID-19 patients. Generally itchy, they are regarded non-specific [102]. In a series of 24 patients, an eruption of small papules, vesicles, and pustules appeared 4 to 30 days after the onset of COVID symptoms and resolved in a median of 10 days [103]. This type of skin manifestation may recur in a limited number of cases.

Other cutaneous manifestations - Less frequently reported dermatologic manifestations include papulo-squamous eruptions, erythema multiforme-like lesions, dengue-like petechiae rashes, and gangrene. An erythematous and polymorphic rash on hands and feet, oral mucositis, and conjunctivitis has been described in a cohort of 10 Italian children during the COVID-19 pandemic [104]. Similar cases have been reported in other studies.

The skin manifestations and disease severity

As the cutaneous manifestations range from benign to those associated with severe disease [105]. The morbilliform rash, the most common cutaneous manifestation of COVID-19 is not linked with disease severity. Similarly, the vesicular varicella-like eruptions associated with SARS-CoV-2 infection, are regarded non-specific. The urticarial rash has been considered a diagnostic clue in early phase of infection and may be associated with more severe form of COVID-19. The retiform purpura and necrotic vascular lesions are associated with severe COVID-19. In general, the pernio-like lesions are associated with less severe COVID-19 infection. But some patients have been found to have recurrent pernio after initial SARS-CoV-2 infection.

With the evolving concepts about Long Covid, the consideration of persistent morbidities related to various organs and systems beyond the acute phase of COVID-19 has dawned. As related to the persistent skin signs and symptoms of COVID-19, urticarial and morbilliform eruptions are relatively ephemeral, whereas papulosquamous eruptions, and particularly pernio, are longer-lasting. It has been analyzed that a previously unreported subset of patients may experience long-hauler symptoms in dermatology-dominant COVID-19, raising issues about persistent dermatological inflammation and affliction in some patients, including those who suffered with relatively mild COVID-19 [106]. The patients suffering with recurrent pernio after initial SARS-CoV-2 infection, can be regarded as having a dermal manifestation of Long Covid. There are no treatment guidelines for COVID-19-associated pernio-like lesions. The use of high-potency topical corticosteroids may be helpful.

Conclusion: prognosis and therapeutics

COVID-19 can now be considered a systemic disease with pulmonary and extrapulmonary manifestations which increase the severity and lethality of COVID-19 and include vascular, cardiac, kidney, gastrointestinal, and central nervous system complications. Further, there is growing evidence that COVID-19 can affect almost every organ, including the skin. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. These mild cases typically recover within two weeks, whereas others may take variable time for recovery. The severity of COVID-19 varies and is a deciding factor for the possible interventions. In turn, age is a deciding factor for severity of the disease [107]. In fact, the organs involvement, severity of the damage, and effectiveness of therapeutic interventions are generally on adverse side in elderly.

There is no specific or effective treatment or cure for COVID-19. The cornerstone of management of COVID-19 is supportive care, which includes treatment to relieve symptoms, fluid therapy, therapy to modify deleterious aberrant and hyper-immune disorder, respiratory support and prone positioning as needed, and medications or devices to support other affected vital organs. The home-based treatment may suffice for the majority, whereas patients with more severe disease may need treatment in hospital. In those with deranged renal function RRT may be required. Those with worsened diabetes or new onset hyperglycemia benefit with monitored insulin treatment. Whereas in those with glucocorticoid deficiency due to HPA axis or adrenal failure low oxygen levels, use of a glucocorticoid, such as dexamethasone is recommended [108]. The dermatological lesions may be given symptomatic treatment, but, in general, are benign and resolve in due course [93].

Presently, various experimental treatments are being actively studied in clinical trials for the severe disease. The past experience with certain drugs or regimen thought to be promising for COVID-19 earlier in the course of the pandemic, such as hydroxychloroquine and lopinavir/ritonavir, was later found to be ill-based. The drugs, especially

hydroxychloroquine and lopinavir/ritonavir were later proved ineffective with potential adverse effects or even harmful [109]. The antiviral remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases *in vitro*, has shown limited evidence of its efficacy when used early in course of the disease. The monoclonal antibody-based therapies may be helpful if used early in the course of the disease in those at high risk of progression to severe disease. Further, it was demonstrated in a randomised clinical trial that the combination of remdesivir with other agents, such as baricitinib may be more effective than remdesivir alone.

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Chapter 7: Exploring Etiopathophysiological Links and Clinical Course of Long Covid

Background

Introduction - the Long Covid syndrome: The post-acute sequelae of COVID-19 (PASC) or 'Long Covid' is a varying, relapsing, and remitting disorder that may follow recovery from acute infection with SARS-CoV-2 in some patients and last for a variable period. It has a protracted course culminating as lingering and incapacitating illness predisposed by certain constitutional factors and comorbidities. Akin to COVID-19, it primarily affects the respiratory system, but other systems such as neurologic, cardiologic, hepatic, renal and pancreatic, and cutaneous systems may be involved. As the infection can harm the immune system, various organs including lungs fall prey to the aberrant immune response.

Etiological correlates and pathogenesis: Long Covid is a multisystem disorder entailing multiple symptoms related to various organs. There are several theories about the etiology of Long Covid such as continuing presence of the virus and its biologically active fragments, reinfection with the same or a different variant, dysfunctional immune reactions leading to a chronic inflammatory state, an ill-defined condition exhibiting symptoms of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) suggestive of a complex, multisystem disorder, post-traumatic stress following severe COVID-19 illness and critical care issues, and aftermath resulting due to disturbed microbiota in gut, lungs, and other organs.

Long Covid pathogenesis -new insights: The SARS-CoV-2 infection activates the humoral immunity leading to formation of antigen-antibody complexes and the antigen-antibody reactions, which may propagate to organ damage. Simultaneously, viral superantigens may overstimulate immune responses, inducing negative feedback loops to hamper immune function and allow the virus to persist and replicate. The persistent virus may contribute to long Covid. There may develop various autoantibodies causing tissue injury and fibrosis in lungs and other organs. The Altered Microbiome leading to the microbial dysbiosis has also been implicated in persisting inflammatory processes culminating as Long Covid.

Conclusion - therapeutic considerations: With expanding awareness, it has been recommended that all patients after recovery from COVID-19 should have access to healthcare. On the practical side, there are being established clinics for people with Long Covid backed by multidisciplinary teams for supportive and specific treatment and follow up. The anti-fibrotic and anticoagulant agents may be helpful in preventing further lung damage and thrombotic episodes. The role of a COVID-19 vaccine in preventing Long Covid is not known, but it may be helpful in reducing morbidity. The strategies to improve the intestinal dysbiotic microbiota through probiotics and microbial transplant appear promising.

Introduction – the Long Covid syndrome

Post Acute Sequelae of COVID-19 (PASC)

The post-acute sequelae of COVID-19 (PASC) or 'Long Covid' is a varying, relapsing, and remitting disorder that may follow recovery from acute infection with SARS-CoV-2 in some patients and last for a variable period. The patients report various symptoms, such as fatigue, dry cough, shortness of breath, headaches, and muscle aches [1]. There are respiratory, cardiovascular, neurological, gastrointestinal, and urological symptoms in unpredictable combinations. In fact, the list of Long Covid symptoms is enormous and Akrami, et al. have reported as many as 205 symptoms in their study of over 3,500 people [2]. The most common symptoms reported in the study were fatigue, post-exertional malaise, and cognitive dysfunction. Further, these symptoms may fluctuate, and there are phases of improvement punctuated with relapse [3]. There is a protracted course of the disease following SARS-CoV-2 infection from acquiring the virus to Long Covid, culminating as lingering and incapacitating illness predisposed by certain constitutional factors and comorbidities (Figure 1).

The SARS-CoV-2 virus primarily affects the respiratory system, affecting and damaging lung alveoli. Simultaneously it causes endotheliitis and microthrombi, enters the blood vessels and may disseminate in the whole body. It also stimulates the inflammatory milieu in the body, causing significant release of cytokines and chemokines leading to cytokine storm in severe cases. The resultant organ damage takes much longer to recover and is responsible for the symptoms of Long-COVID-19. There is a diversity of human response to the SARS-CoV-2 virus, variable course of COVID-19 illness, and a puzzling array of symptoms of Long Covid. The response to the virus and the disease course, depend on various

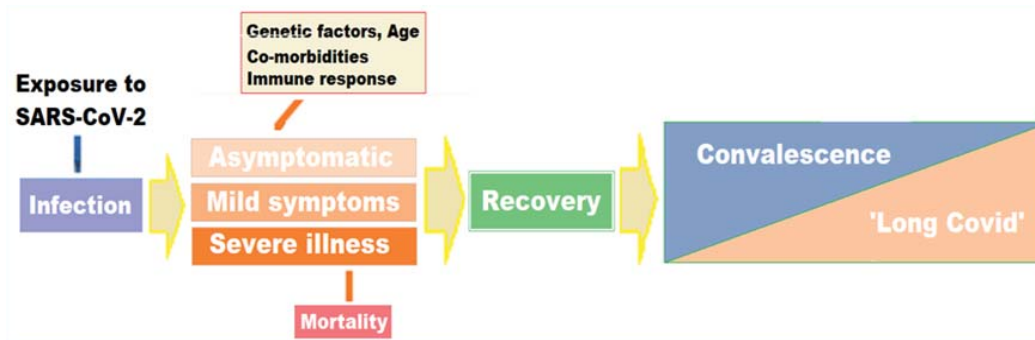


Figure 1: Protracted course of COVID-19 from acquiring the virus to lingering and incapacitating Long Covid.

factors including the constitutional factors including the individual immune status, genetic make-up, and presence of comorbidities. These differences could make certain persons more susceptible to Long Covid [4].

Incidence and prevalence of Long Covid

The UK Office for National Statistics (ONS) considers Long Covid as persistence of various symptoms for more than four weeks. The UK ONS in a survey, which encompassed over 20,000 COVID-19 patients with +ve test, the prevalence was ~20% at four weeks to ~12% after a period of 20 weeks [5]. Curtailing the virus exposure through lockdown measures can effectively reduce the prevalence of COVID-19 as well as Long Covid [6]. As per a rough estimate, over 10% of those infected with SARS-CoV-2 may suffer with Long Covid, which is more common in women than in men. As per the Post-Hospitalisation COVID-19 study (PHOSP-COVID), 23% of women and 19% of men still had symptoms 5 weeks after infection. Further the prevalence has been estimated to be about 20% - 30% in those who were not admitted to hospital, with at least one enduring symptom one month later and about 10% three months later. For others having been admitted to hospital, it was 50% - 89% with at least one enduring symptom after two months. In other studies, it has been highlighted that the incidence and prevalence of Long Covid is not predicted by severity of preceding COVID-19 illness [7].

The men with positive COVID-19 test are more likely to suffer with a severe form of the disease, whereas women with a positive test are more likely to get the ongoing symptoms in form of Long Covid. The current data suggest that 70% - 80% of people experiencing severe acute forms of COVID-19 are men, whereas 70% - 80% of those suffering from Long Covid are women [8]. In addition, there is a distinctive age distribution and Long Covid is most common in middle-aged people, the prevalence has been reported 25.6% at 5 weeks for those between 35 and 49 years old, and less common in younger people and older people. Among the younger people, such as children aged 2-11, about 9.8% of those who test positive for the virus may have lingering symptoms after at least 5 weeks [9]. There are studies to indicate that the children may suffer with Long Covid [10].

The enduring effects of Long Covid

Effects on respiratory system: The COVID-19 begins as a respiratory disease. Clinically, Long Covid is multi-system inflammatory syndrome (MIS). There may occur delayed manifestations of MIS, due to dysregulated adaptation in various organs. The inflammatory process is manifested as increased CRP, D-Dimer, LDH, Ferritin, and IL-6 [11]. It has been documented that the lung damage gradually reduced over two weeks. Certain COVID-19 patients continue to suffer with fatigue, respiratory and other symptoms long after the recovery period. In fact, a follow up study of hospitalized COVID-19 patients documented that even over 70% of them were having shortness of breath a month after discharge and 13.5% were using oxygen at home [12]. Further, there is evidence from previous coronavirus outbreaks, especially the severe acute respiratory syndrome (SARS) epidemic, suggests that the effect may last for a variable period and symptoms may linger for years. A study recorded long-term lung damage in SARS caused by SARS-CoV-1 recorded that even after 15 years, 4.6% of the hospitalized patients still had visible lesions on their lungs, and 38% had reduced diffusion capacity [13].

Gholamrezaezhad, et al. tracked patients using CT scans to study their lungs and found that lung scans were helpful. They followed up on 33 of them for over a month later and found that more than one-third had tissue death that has led

to visible scars. The analysis of lung CT images of these 919 patients from published studies has reported that the lower lobes of the lungs are the most frequently damaged [14]. An Austrian study noted that lung damage lessened with time and 88% of participants had visible damage 6 weeks after being discharged from hospital, but by 12 weeks, this number had fallen to 56%. Defective pulmonary gas exchange, detected through xenon gas radio-diffusion study [15].

Effects on other systems: COVID-19 primarily strikes the respiratory system, but as various tissues also harbour the ACE2 receptors, other organs such as heart, brain, and kidneys are also involved. COVID-19 can affect multiple organs such as neurologic, cardiologic, hepatic, renal and pancreatic, and cutaneous systems. As the infection can harm the immune system, various organs including lungs fall prey to the aberrant immune response. Further, some patients recovered from COVID-19 are left with a weakened immune system and decreased immune-system activity leading to a multitude of after-effects [16,17].

The heart and vasculature are particularly susceptible for over-reactive immune system. During the acute phase of COVID-19, about one-third of patients show cardiovascular symptoms. Some patients also have pulmonary thrombosis. There can result vasculitis, myocarditis, and cardiomyopathy [18]. The patients having pneumonia may be at increased risk of cardiovascular disease 10 years later, as shown by the SARS and MERS data [19]. Many patients experience neurological complications due to inflammation or the virus infecting the brain, such as chronic fatigue, delirium, and the cognitive difficulties, including confusion and memory loss, persisting for a variable period after the acute phase.

Etiological correlates and pathogenesis

The exact cause(s) of the PASC or Long Covid is presently unknown, but the syndrome is likely to have multiple triggers and involve multiple conditions with different associations [8]. With multiple symptoms related to various organs, it seems logical to conclude that long COVID is a multisystem disorder entailing multiple mechanisms [20]. In fact, the etiology of Long-COVID-19 seems to be a continuum of the disease pathogenesis of acute illness. There is likely to be tissue damage due to altered microenvironment due to a sudden spurt in inflammasomes and cytokines. The tissue damage also occurs due to hypoxia and oxidative stress.

There have been sponsored several theories about the cause of Long Covid such as continuing presence of the virus and its biologically active fragments, reinfection with the same or a different variant, dysfunctional immune reactions leading to a chronic inflammatory state, an ill-defined condition exhibiting symptoms of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) suggestive of a complex, multisystem disorder, post-traumatic stress following severe COVID-19 illness and critical care issues, and aftermath resulting due to disturbed microbiota in gut, lungs, and other organs (Figure 2). The search for the etiological factors of Long Covid aims to help in its prevention as well as design therapeutic strategies. Further, the understanding of the pathophysiology of Long-COVID-19 is important to predict, prevent and treat long-term consequences of COVID-19.

Persistence of virus and viral fragments

Following the acute course of COVID-19, the SARS-CoV-2 virus may persist and continue to replicate in cells expressing ACE2 receptors such as endothelial cells. The persistent virus infection could induce both cell damage and direct activation of dendritic cells, which could lead to autoimmunity. In fact, a persistent infection could explain various symptoms of long COVID. Salmon-Ceron, et al. have reported people who had tested positive for COVID-19 and whose symptoms had either lasted longer than two months from initial onset or had recurred [21]. They found that 25% still had positive PCR nose and throat swabs.

Etiopathogenesis of Long Covid: The Emerging Concepts

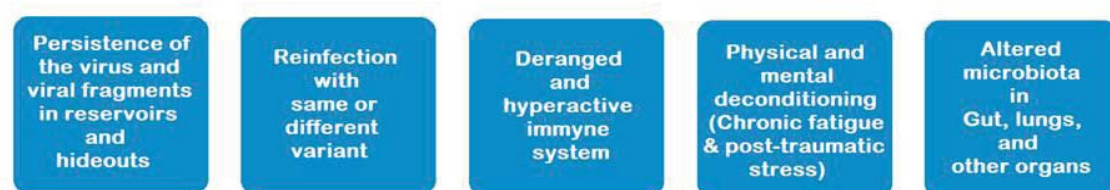


Figure 2: The emerging concepts for etiopathogenesis of Long Covid – the damage to tissues and organs occurs due to direct toxicity of the virus and viral fragments, injury to organs and vasculature due to inflammatory processes and hyperimmune response, dysregulated RAS activity, hypercoagulability, and altered microbiome.

Liotti, et al. used PCR tests with patients discharged from an Italian hospital deemed to have recovered from COVID-19 and found 17% tested positive [22]. Referring to a number of other publications, Yong's (2020) preprint also reported that some patients still tested positive for COVID-19 four months later. They also noted the virus has been detected in faeces for up to two months regardless of gastrointestinal symptoms. A persistent virus infection could induce both cell damage and direct activation of dendritic cells, which could lead to autoimmunity. In fact, a persistent infection could explain various symptoms of long Covid. Further, the continuing morbidity may be partly due to a persistent systemic infection indicated by continued virus RNA shedding [23].

Further, if the virus itself is not at work, there is evidence that fragments of the virus, the genomic bits, and the viral non-structural proteins (NSPs) and structural proteins (SPs), can persist for months, might disrupt the body in certain ways even though they cannot infect the cells [24]. It has been suggested that in certain cases, the viral persistence may lead to a specific immune response responsible for Long Covid symptoms. The autoantibodies play a part, with the immune system attacking the various tissues and organs harbouring the viral reservoirs or lingering fragments of viral RNA or proteins contributing to the persisting Inflammatory process leading to pericarditis and/or myopericarditis, and inflammation of olfactory bulbs occasionally found in case of persistent or recurrent anosmia.

Further, the SARS-CoV-2 genome has been found in respiratory cells, cells lining the blood vessels, and the syncytia, in Long Covid patients. These histopathologic changes, persistence of the abnormal cells, and the virus-infected cells may be linked with continuance of ongoing viral replication and organ damage, and persistence of Long Covid symptoms in those recovered from the disease. Similarly, the SARS-CoV-2 fragments have been found in interstitial cells of the myocardium along with inflammatory changes [25]. In another study, Maiese, et al. have reviewed major autopsy findings associated with CVS in COVID-19 patients from 28 published studies involving 341 cases. They found severe direct endothelial injury associated with intracellular virus, multifocal necrosis, interstitial inflammatory infiltration, myocarditis, pericarditis, and myocardial hypertrophy, along with lymphocytic endotheliitis in various organs such as lung, kidney, liver, and small intestine [26].

Deranged and hyperactive immune system

The deranged and hyperactive immune system is another likely mechanism which entails damaging effects on various tissues and organs. There occurs tissue damage in various organs due to altered microenvironment following altered immunity and perturbed inflammatory Response. Simultaneously, the inadequate immune response may also lead to an auto-inflammatory chronic condition in a genetically predisposed individual [21]. From an immunologic perspective persistent infection and autoimmunity are two distinct mechanisms that could be caused by SARS-CoV-2. Further, Long Covid symptoms may be explained by immune-mediated autonomic instability resulting in physical deconditioning leading to muscle weakness, cardio-respiratory impairment, hypovolaemia, and neuropathy [27]. The inflammatory changes seen in COVID-19 may result in inflammation of blood vessels, myocarditis and arrhythmias which may explain various symptoms and findings in Long Covid [28].

The lung damage and reduced exercise tolerance have been correlated with serum markers of inflammation and mitochondrial stress. Betty Raman, et al. prospectively studied 58 COVID-19 patients post-hospital discharge and 30 comorbidity-matched controls for multiorgan (brain, lungs, heart, liver, and kidneys) magnetic resonance imaging (MRI), spirometry, six-minute walk test, cardiopulmonary exercise test (CPET), quality of life, cognitive and mental health assessments. The study found that at 2-3 months from disease-onset, 64% of patients experienced persistent breathlessness and 55% complained of significant fatigue. On MRI, tissue signal abnormalities were seen in the lungs (60%), heart (26%), liver (10%) and kidneys (29%) of patients [29]. The microvascular damage may also be a cause of persistent organ damage in patients with enduring symptoms. The autopsy findings suggest that focal damage of the microvascular pulmonary circulation due to the SARS-CoV-2 virus infection may also be the cause of persistent lung damage in patients who recover from severe COVID-19 [30].

Evans, et al. studied 1,077 COVID-19 patients, recording symptoms including physical impairments, mental-health difficulties such as anxiety, and cognitive impairments in areas such as memory and language [9]. The researchers also recorded basic information such as age and sex, and biochemical data such as levels of C-reactive protein as a measure of inflammation. The cluster analysis is a mathematical tool to analyze and record identifiable groups of patients with similar epidemiological profiles. The PHOSP-COVID Collaborative Group working to correlate is evidence of inflammation, cardiovascular affliction, and other changes [9]. Other studies have also documented altered levels of cytokines in the

blood samples of Long Covid patients, suggesting the derangement of immune system as well as proinflammatory markers [31].

Chronic fatigue and post traumatic stress

As such, it is not uncommon for an infection to trigger long-lasting symptoms. A study of 253 people diagnosed with certain viral or bacterial infections found that after 6 months, 12% reported persistent symptoms including disabling fatigue, musculoskeletal pain, neurocognitive difficulties, and mood disturbance [32]. In fact, the percentage is akin to the Long Covid prevalence observed in the United Kingdom by the ONS. Some people with Long Covid may look similar to the ME/CFS but striking difference is that people with Long Covid are more likely to report shortness of breath than are those with ME/CFS [33]. The long Covid is, thus, an umbrella term and there are multiple syndromes under this coalition.

One of the most insidious long-term effects of COVID-19 is severe fatigue manifesting as crippling exhaustion and malaise following recovery from acute infection. In an Italian study involving 143 post-discharge COVID-19 patients, 53% reported fatigue and 43% had shortness of breath for over 2 months [1]. Another study showed that 25% of patients in China had abnormal lung function after 3 months, and that 16% were still fatigued [34]. These symptoms resemble chronic fatigue syndrome, also known as myalgic encephalomyelitis (ME). There are no known biomarkers and diagnosis is based on symptoms.

The clinical condition bears similarity to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which was observed after SARS epidemic in Hong Kong. A follow-up study of 233 patients infected with SARS showed that 27% of the patients suffered with ME/CSF [35]. Similarly, in another study, 22 people who recovered from SARS in Toronto still suffered fatigue, aches, depression and altered sleep patterns one to three years later [36]. It was suggested that the symptoms might result from lingering inflammation after the virus was gone, as well as the psychological trauma of the infection.

A subset of patients with prolonged COVID-19 symptoms have been shown to have similarity with ME/CFS [37]. The most commonly reported incapacitating symptom following the COVID-19 is fatigue. A similar symptom occurs following viral infections and was noted after the Spanish Flu pandemic and the more recent SARS, MERS, and Ebola epidemics. Finally, there is possibility of the post-traumatic stress induced by the COVID-19 illness which can be exacerbated by intensive health care (post-intensive care syndrome) received especially for severe or critical disease. The post-traumatic stress can precipitate mental deconditioning, especially in those with previous history of anxiety, depression, insomnia, or other mental health difficulties. The mental deconditioning may be accompanied by physical deconditioning due to a lack of exercise while ill and later during recovery.

The reinfection with same or different variant

The hypothesis about reinfection with Same or Different Variant of SARS-CoV-2 has been propagated to explain the persisting symptoms in Long Covid. The partial and/or short-lived immunity, and immune suppression, as induced by its superantigens, also plays a crucial role in reinfection and establishing persistent SARS-CoV-2 infections. Evidence for persistent infection has been indicated by prolonged viral shedding in feces in several studies. Reactivation or reinfection of the SARS CoV-2 is a concern associated the Long Covid. One likely explanation for reinfection is waning of neutralizing antibodies within 2–3 months following recovery from SARS-CoV-2 infection. Serial antibody estimation and evidence of active viral replication can indicate the reinfection. The reinfection may entail lingering Long Covid symptoms as well as the probability that some of the Long Covid patients may also act as the carriers of the virus. In this respect, the notions of virus persistence, viral reservoirs, chronic viral shedding, and related aspects are important.

The occasional cases of reinfection occur but the possibility of a significant number of reinfections leads us to the possibility existence of SARS-CoV-2 Viral Reservoirs. In general, subset of persistent viruses can go latent, when the viruses disappear, leaving their genetic material to re-emerge later. Even after two months following the infection, SARS-CoV-2 mRNA, SPs and NSPs have been detected in the intestines of those infected. Further, four months after onset of COVID-19, immunofluorescence and PCR analysis of intestinal biopsies show persistence of viral RNA and protein [24]. The immune system is likely to react these remnant proteins. The concept of potential viral reservoirs is captivating, as several viral infections are known to lie in body reservoirs, such as Ebola and hepatitis B. Experimentally, when a mouse is infected with murine coronavirus which infects the liver and the CNS, viral RNA can persist in its central nervous system (CNS) without being infectious. Further, the RNA can remain for the mouse's whole lifetime, and associated with demyelinating disease.

In the persistent infection, SARS-CoV-2 virus is dispersed into various organs, and it is common for these patients, to test negative for viral genes, then test positive again as they shed low amounts of viral RNA. Further, the tests for COVID-19 may detect a scrap of the viral genome, which may last as long as 15 weeks. The COVID-19 patients with mild or asymptomatic disease were more likely to be persistently PCR positive than participants with a more severe illness. However, higher total antibodies levels associated with persistent viral RNA shedding may not increase the transmission risk [38]. Further, fully recovered individuals with persistent viral RNA shedding are unlikely to be a significant source of SARS-CoV-2 transmission and seem to have a more durable immunity, strongly reducing the risk of re-infection.

The persistent virus infection implies persistent superantigen exposure, which in turn induces systemic inflammation leading to cardiovascular morbidity and development diabetes, documented following COVID-19. In addition, diabetes and cardiovascular disease worsen the outcome in case of reinfection, predispose for residual inflammation and development of autoimmune reaction. The reinfection may be an interesting proposition, however, the difference in clinical profile between the initial manifestations of COVID-19 and the prolonged symptoms in Long Covid fails to support this hypothesis.

The altered microbiota in gut and other organs

The human gut harbours a huge population of enteric microbiota, majorly dominated by Bacteroidetes and Firmicutes that produces several metabolites to maintain the gut homeostasis. The gut microbiota plays important roles such as vitamin synthesis, protection against pathogens, and development and maturation of host immune system. Diet, environmental factors, and genetics play an important role in shaping gut microbiota. Gut microbiota diversity is decreased in old age. Any deviation from normal gut microbial composition is defined as microbial dysbiosis and characterized by preponderance of pathobionts and decline in the populations of the key taxa like Bacteroidetes and Firmicutes. The gut microbiome has been shown to influence the immune system response to COVID-19 infection and potentially affect disease severity and outcome.

Although COVID-19 is primarily a respiratory illness, there is mounting evidence to suggesting that the gut microbiome is involved in its clinical manifestations. The gut microbiome influences on the immune system in general and may potentially affect COVID-19 severity, course, recovery, and outcome in form of Long Covid.

Besides the gut, other organs such as lungs also harbour *Fusobacterium*, *Haemophilus*, *Prevotella*, *Streptococcus*, and *Veillonella* as main genera, which are relatively small as compared to the enteric microbiota. The emergence and maintenance of lung microbiota is governed by the equilibrium between microbial migration from the upper respiratory tract and microbial removal by the host defense systems. Even in small concentrations, the airway microbiome is crucial to the host immunity. The gut-lung axis also involves the migration of immune cells from gut to respiratory tract through circulation. The gut may regulate the responses in lungs via host-acquired inflammatory mediators in the circulation. Further, the lungs and the gut are intricately linked and affect the homeostasis through existence of an immunological co-ordination between the gut and lungs.

It has been documented that gut microbiota composition is significantly altered in patients with COVID-19 compared with non-COVID-19 individuals irrespective of the medication received [39]. Several gut commensals with known immunomodulatory potential such as *Faecalibacterium prausnitzii*, *Eubacterium rectale* and *bifidobacteria* have been shown to be underrepresented and low in samples collected up to 30 days after recovery from acute COVID-19. Further, the altered composition was related with disease severity and elevated concentrations of inflammatory cytokines and serum markers such as C reactive protein, lactate dehydrogenase, aspartate aminotransferase and gamma-glutamyl transferase. Further, in a subset of recovered patients with COVID-19 experiencing persistent symptoms, such as fatigue, dyspnoea, and joint pains, the gut microbiome was shown to be dysbiotic 80 days after initial onset of symptoms [39].

There has been shown association between gut microbiota composition, levels of cytokines and inflammatory markers in patients with COVID-19 suggesting that the gut microbiome is involved with the disease severity as well as outcome via modulating the immune responses. The gut microbial dysbiosis persists after the disease resolution, partly because of the medications given during the acute phase and could contribute to the persistent Long Covid symptoms.

Long covid pathogenesis - new insights

Superantigens hypothesis and histological correlates

There seems a possibility that the virus may be entering into blood vessels in its earliest phase when infecting the nasal

and oral mucosa, and pharynx, and traversing to infect the olfactory bulb on the inferior surface of the brain supported and protected by the cribriform plate, leading to anosmia and dysgeusia. Another extrapulmonary manifestations in COVID-19 is the formation of antigen-antibody complexes by 2-3 weeks, which activate the humoral immunity. The antigen-antibody reactions may propagate to organ damage leading some patients continue to suffer from long Covid symptoms after clearing the infection. Simultaneously, viral superantigen may overstimulate immune responses, inducing negative feedback loops, that hamper the immune function and allow the virus to persist and replicate. The SARS-CoV-2 superantigens are known to cause a strong immune response and cytokine storm, by a polyclonal T cell activation.

The orchestration of antigen-specific immune responses is important in understanding the concepts related to antigens and superantigens. In a normal physiological situation, the viral antigens are presented by Dendritic cells (DCs) to T lymphocytes leading to activation of T cells with an antigen-specific T-cell receptors (TCRs). The activation of specific T cells leads to clonal expansion for antigen-specific T-cell population resulting in effective clearance of the virus. In an aberrant pathophysiological situation, superantigens are presented by DCs to T lymphocytes and leads to activation of a large subgroup of T lymphocytes through their common receptors. The large groups of activated T cells have clonal expansion leading to immune overreaction [40]. In a favourable situation, the immune response is downregulated by negative feedback loops involving CD4+CD25+ Treg lymphocytes and IL-10. The protective down-regulation of superantigen responses occurs naturally and the superantigen-induced immune reactions are checked for generating immune hyper-response. The down regulation of the immune system by corticosteroid treatment may also lead to immune suppression through down-regulating of the superantigen response to reduce morbidity and mortality in severe COVID-19 [23]. The downregulation of superantigen response, naturally or as result of corticosteroid treatment is likely to result in a partially effective immunity allowing the virus to persist.

There may occur/develop various autoantibodies during the course of COVID-19. In single-center and retrospective study from Huanshi, China involving 8 severe and 13 critical cases of COVID-19, demonstrated anti-52 kDa SSA/Ro antibody, anti-60 kDa SSA/Ro antibody, (SSA = Sjögren's-syndrome-related antigen A), and antinuclear antibody (ANA) in 20%, 25%, and 50% of patients, respectively [41]. The autoantibodies may aggravate the ongoing damage and fibrosis in lungs and lead to other long-term consequences occurring in Long Covid patients. The immune dysregulation may also be responsible for the prothrombotic state and its related conditions in COVID-19. In addition, endotheliitis and hypoxemic tissue injuries may play a part apart from antigen-antibody reactions and aberrant immune response. This is also endorsed by histopathological correlates of COVID-19 showing extensive alveolar damage, thrombosis of the lung micro- and macro-vasculature, pneumocytes and endothelial cells showing viral RNA, and presence of syncytial cells [42].

The altered microbiome and immunologic correlates

The gastrointestinal (GI) tract is the largest immunological organ in the body and gut microbiota influence immune responses. Further, the ACE2 receptors are widely expressed in the gut enterocytes and the amino acid transport function of ACE2 has been linked to gut microbial ecosystem. The SARS-CoV-2 infection is, thus, bound to affect the gut microbiome and enteric milieu, which in turn influences the severity of COVID-19 as well as the magnitude of the immune system response to the infection. The elderly, immune-compromised patients, and patients with other co-morbidities like type-2 diabetes, cardiovascular disorders have a general imbalance of gut microbiota (dysbiosis) and fare poorly in combating COVID-19 [43].

Various studies have noted persistent alterations in the fecal microbiome during the hospitalization and later, as compared with controls. Considering this, the alteration in the variety and volume of bacteria in the gut, leading to the microbial dysbiosis may also be implicated in persisting inflammatory symptoms following recovery from COVID-19, or Long Covid. Further, various studies have identified the viral RNA of SARS-CoV-2 in fecal specimens [44]. Further, the fecal microbiota alterations have been associated with fecal shedding of SARS-CoV-2 genome and COVID-19 severity. Another study noted that though about 12% of patients with COVID-19 will manifest GI symptoms, SAR-CoV-2 shedding was observed in 40.5% of patients [45]. Further, the viral genome has been identified from anal/rectal swabs of the COVID-19 patients even after the clearance of virus from the upper respiratory tract [46].

In an oft-quoted study, Yeoh, et al analysed the blood and stool samples and medical records from 100 hospital in-patients who had tested positive for COVID-19 and from 78 people without COVID-19, as controls. The serial faeces samples were collected up to 30 days after the virus was no longer detected in nasal and throat swabs. The gut microbiome, in respect of both the taxa and range of microorganisms, was found to be significantly altered compared with people who

had not had COVID-19. The analysis suggested that Gut microbiome composition was significantly altered in patients with COVID-19 compared with non-COVID-19 individuals irrespective of whether patients had received medication. Several gut commensals with known immunomodulatory potential such as *Faecalibacterium prausnitzii*, *Eubacterium rectale* and *bifidobacteria* were reduced in COVID-19 patients and remained low up to 30 days after disease resolution [39]. There appear to exist a direct bidirectional relationship between the COVID-19 virus and the gut and lung microbiomes [47].

The pattern also exhibited correlation with disease severity and elevated concentrations of inflammatory cytokines and other markers such as C reactive protein, lactate dehydrogenase, aspartate aminotransferase and gamma-glutamyl transferase. The association between gut microbiota composition, levels of cytokines and inflammatory markers in patients with COVID-19 suggest that the gut microbiome is involved in the magnitude of COVID-19 severity possibly via modulating host immune responses. In a subset of recovered patients with COVID-19 experience persistent symptoms, such as fatigue, dyspnoea, and joint pains, some over 80 days after initial onset of symptoms, the dysbiotic gut microbiome could contribute to immune-related Long Covid symptoms. It was inferred that the altered microbiome was associated with enhanced values for inflammatory markers in suggesting that the microbial dysbiosis may contribute to Long Covid symptoms.

In another study, Zuo, et al. found that patients with COVID-19 had significant alterations in fecal microbiomes compared with controls, characterized by enrichment of opportunistic pathogens and depletion of beneficial commensals, at time of hospitalization and later. The depleted symbionts and gut dysbiosis persisted even after clearance of SARS-CoV-2 and resolution of respiratory symptoms. Further, the baseline abundance of *Coproccillus*, *Clostridium ramosum*, and *Clostridium hathewayi* correlated with COVID-19 severity, and there was an inverse correlation between abundance of *Faecalibacterium prausnitzii* (an anti-inflammatory bacterium) and disease severity [48].

The gut microbiota derived signals are known to tune the immune cells for pro and anti-inflammatory responses thereby affecting the susceptibility to various diseases. In SARS-CoV-2 infection also, a healthy gut microbiome is pivotal in maintaining an optimal immune system to prevent an array of excessive immune reactions that eventually become detrimental to lungs and other vital organs. Like the gut microbiota, there is presence of distinct microorganisms in the lungs predominantly while *Bacteroidetes*, *Firmicutes*, and *Proteobacteria*. Interestingly, the gut microbiota has been shown to affect pulmonary health through the bidirectional gut-lung axis. Various respiratory viral infections including SARS-CoV-2 cause perturbations in the gut microbiota, and in turn the disease course is influenced by gut microbiome [49].

Conclusion: the therapeutic considerations

Right now, our understanding about both COVID-19 and Long Covid is expanding. The COVID Human Genetic Effort aims to find genetic variants that compromise people's immune systems and make them more vulnerable to the virus [50]. The study plans to include those with long-term impairment, hoping to understand why their symptoms persist and to find ways to help them. The virus can also have the opposite effect, causing parts of the immune system to become hyperactive and trigger harmful inflammatory activity.

The issue of having a lingering form of the disease was started on social media like Facebook group for people with long COVID. Today, it has moved from being a curiosity, to a recognized public-health problem. In January 2021, the World Health Organization revised its guidelines for COVID-19 treatment to include a recommendation that all patients should have access to follow-up care in case of Long Covid [51]. On the practical therapeutic side, some countries are already opening clinics for people with Long Covid. There is a growing consensus that the long Covid clinics should be backed by multidisciplinary teams for supportive and specific treatment and follow up (Figure 3).

The trials suggest that anti-fibrotic and anti-inflammatory agents such as pirfenidone, deupirfenidone (the selectively deuterated form of pirfenidone), and Nintedanib may be helpful. Other drugs like, apixaban, an anticoagulant that might reduce the risk of dangerous blood clots; and atorvastatin, an anti-inflammatory may be helpful. Finally, the role of COVID-19 vaccines in preventing Long Covid is not known, although they may be helpful in preventing death and severe illness. Further, the impact of vaccines in people who are already having Long Covid is also not known. In a UK survey of more than 800 people with Long Covid, it was reported that 57% saw an overall improvement in their symptoms, 24% no change and 19% a deterioration after their first dose of vaccine [52].

The strategies to improve the intestinal dysbiotic microbiota may be helpful in reducing severity in COVID-19 and

The Long Covid Healthcare Continuum



Figure 3: The Long Covid healthcare continuum – diagnosis and Clinical workup, Investigations, assessment of organ damage and dysfunction, and Supportive and specific treatment.

Long Covid. The prebiotics and probiotics may be helpful [53]. Further, the adjunctive therapies based on the modulation of the gut-lung axis and re-establishment of eubiosis could be an important therapeutic approach for constraining the harmful consequences of COVID-19 [54]. The microbiome transplants may hold promise for Long Covid and have been proposed as a potential treatment for individuals suffering long-term incapacitating symptoms [55].

In the United Kingdom, the Post-Hospitalisation COVID-19 Study (PHOSP-COVID) aims to follow 10,000 patients for a year, analyzing clinical factors such as blood tests and scans, and collecting data on biomarkers [56]. It is a consortium of leading researchers and clinicians from across the UK to understand and improve long-term health outcomes for confirmed or suspected COVID-19 patients. Currently the information is limited concerning the long-term effects of COVID-19 and the ongoing medical, psychological and rehabilitation needs for these patients. The PHOSP-COVID team aims to develop trials of new strategies for clinical care to improve their long-term health. A similar study of such patients for has been launched in the United States.

There is evidence that SARS-CoV-2 virus may induce neurological impairments by invading the central nervous system leading to chronic myalgias and certain neurological deficits. The COVID-19 survivors from ICU care are likely to manifest various psychological, physical, and cognitive impairments. The Long Covid may results in a relevant morbidity for 3–6 months, and rehabilitation services and dedicated Long Covid healthcare might be needed for more than 12 months [57]. There are recommendations that the rehabilitation should commence in the critical care setting to prevent neuromuscular complications and improves functional status in later during Long Covid phase.

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Postscript: The Ongoing Pandemic: Compromised Health, and Confined and Restricted Human Life

The SARS-CoV-2 infection and COVID-19 pandemic

The current ongoing pandemic of COVID-19 caused by SARS-CoV-2, is associated with high morbidity and mortality in several countries across the globe. A prompt and effective detection of the disease is crucial to identify those infected, to monitor the infection from epidemiological perspective, and to take measures for its containment. On the other hand, the early diagnosis and efficient treatment of COVID-19 including newer therapeutic modalities such as monoclonal antibodies against SARS-CoV-2, may contribute to the individual clinical improvement and limit the morbidity and mortality in the society at large. The likely course of COVID-19 pandemic not certain, and the pandemic being considered a major health hazard, may continue in the foreseeable future or may with low or moderate level of transmission become endemic. The COVID-19 vaccines bear hope to bring COVID-19 pandemic under control, paving a way for its endemism [1]. In this respect, the WHO in a recent communique indicated that COVID-19 in various countries including India may be entering some kind of stage of endemism with low or moderate level of transmission [2].

The effects and fallouts of COVID-19 pandemic are striking as it has impacted the social, economic, political, and healthcare aspects of human life. The pandemic is being considered a major health hazard that may continue to afflict human life in the foreseeable future. The transformation of life, thus, at the individual level as well as at the community and collective levels, seems inevitable. Another aspect of the COVID-19 pandemic is the unprecedented levels of misinformation, rumours, and conspiracy theories related to COVID-19 relayed and reproduced by lay and social media, dubbed 'infodemic' by the WHO, which are counterproductive to the fight against the pandemic in the short and long term. There are concerns about low to middle income countries (LMICs) related to the COVID-19 preparedness, knowledge sharing, intellectual property rights, and environmental health together with the serious constraints regarding readiness of health care systems to respond to the pandemic. In fact, the spread of COVID-19 presents an extraordinary ethical dilemma for resource constrained nations with poorly developed health and research systems.

In the current crisis, sharing of scientific knowledge and technology has an important role to play. In addition, emergency preparedness is a shared responsibility of all countries with a moral obligation to support each other [3]. The ongoing pandemic has led to a situation in which the scale of emergency is similar to WW-II, requiring decisiveness and commitment. In LMICs, the greatest challenge is to design strategy for early response to COVID-19 outbreaks. South Asia holds a quarter of the world's population with currently COVID-19 affected countries including Afghanistan, Pakistan, India, Nepal, Bangladesh, and Sri Lanka which may have severe constraints in management of the pandemic. In fact, the current low number of reported cases from these areas is likely to be due to less testing with limited resources in these countries. The resource allocation should be rational, transparent, and based on scientific evidence as the current COVID-19 crisis presents challenges that are beyond and above the earlier outbreaks. Efforts for developing and supplying medical devices, diagnostic tools, vaccines, therapeutics, and other medical technologies for COVID-19 pandemic should be tackled judiciously.

Restricted human life and compromised health

The SARS-CoV-2 Infection control measures are recommended to prevent exposure as well as reduce transmission of the infection include the personal preventive measures at individual level such as mask-wearing, diligent hand washing, particularly after touching surfaces in public, respiratory hygiene (covering the cough or sneeze), avoiding touching the face (in particular eyes, nose, and mouth), cleaning and disinfecting objects and surfaces, and ensure adequate ventilation of indoor spaces. Apart from the mask-wearing decreasing exposure to the infection, has also been hypothesized to reduce the viral load when exposed, and hence to reduce the risk of severe illness [4]. There are other public health measures apart from personal preventive measures for infection transmission reduction focused for source control and containment of infection and include social/physical distancing, stay-at-home orders, school, venue, and nonessential business closure, bans on public gatherings, and travel restrictions with exit and/or entry screening.

The preventive measures are supplemented with aggressive case identification and isolation and contact tracing and quarantine. In the containment areas, the residents are encouraged to stay alert for symptoms and practice appropriate measures to reduce further transmission. The widespread testing and quarantine strategies are imposed to quickly identify secondary infections in an exposed individual and reduce the risk of exposure to others. There are

strategies involving self-quarantine at home, with maintenance of at least six feet (two meters) distance from others at all times. There are variations about preventive and quarantine measures for vaccinated and unvaccinated individuals, and those with a recent history of SARS-CoV-2 infection. All these measures restrict human interactions and social and economic activities. The COVID-19 pandemic has thus imposed multiple restrictions on human life, with added risks to unprecedented morbidity and mortality, compromising the global human health, in general [5].

The COVID-19 pandemic has profoundly changed the human life, caused tremendous human suffering, and challenged the basic foundations of socioeconomic well-being, beyond the immediate impacts on health. The short and long-term impacts are likely to be severe for the disadvantaged groups such as older people, children, and women in LMICs. The COVID-19 outbreak poses significant challenges for the elderly, who have high risks for serious complications which can significantly deteriorate their functioning, health status, and social connections. The closure of schools and home confinement during health pandemics has enduring effects on child and adolescent psychological well-being. In today's increasingly urban world, the cities may be better equipped than the rural areas to respond to the COVID-19 crisis as the latter vastly lack health care facilities. The COVID-19 will, thus, have a negative impact on various dimensions of human life and the potential for deeper effects with GDP and average household income falling by over 10%, unemployment rising by 5 percentage points and life expectancy dropping by half a year.

The evolving healthcare options and innovations

The COVID-19 pandemic has been a reality check for various provisions of healthcare available in different countries, including the preventive and therapeutic, outdoor consult as well as indoor and intensive care. Whereas in China, the totalitarian regime was able to deal with the pandemic with an iron hand, fully bifurcate COVID-19 healthcare from that for non-COVID-19, and ably carry out preventive measures and vaccination program, in other countries situation has been different. The public health surveillance programs and available infrastructures were shown as not consistently optimal. Additionally, the existing healthcare facilities were unable to cope with the sudden surge and manage intense pressure on their workload especially in the settings of acute care. Even with contingency plans well laid out, healthcare systems were incapable to cope with the abrupt surge in demand and needed to be transformed. The COVID-19 pandemic, thus, has acted as a transformation catalyst, accelerating the implementation and adoption of changes in healthcare. The emerging prototypes of healthcare delivery appear to put more emphasis on preventive measures, remote care, and utilization of innovative digital technologies.

The Hospital-at-Home (HaH) concept was already making inroads in the conventional hospital-based healthcare approach for a large number of diseases, with the hospice service being a surrogate example. In fact, it is being dubbed as the next frontier in the healthcare delivery and our experience with the pandemic has fast accelerated the HaH programs. The emerging HaH programs have advantage of lower costs and readmission rate, while maintaining quality and safety levels, and better patient experience. Build on the HaH concepts, the conditions can be identified and progressively dispensed with home-based primary and secondary care (Figure 1).

Similar to the scenario in various sectors, the health services and healthcare too have had profound impact owing to COVID-19 pandemic. The COVID-19 pandemic has brought home the realization that a significant proportion of healthcare

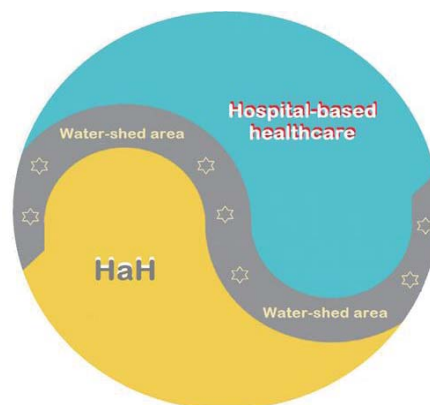


Figure 1: The conventional hospital-based healthcare, the HaH and the water-shed area for intermediate health conditions.

activities can be tendered remotely equally effectively through technologically empowered approach. As related to the healthcare, there are certain salient aspects likely to emerge in the post-COVID-19 era -

There is shifting of large number of patients to remote care. The telehealth services have already been used in emergencies and during crises in the past. With possibility of quality transfer of data, audio and video communications during the COVID-19 pandemic, their utilization has widely accelerated. The pandemic has become a catalyst for swift implementation of online consult and therapy, replacing the clinician/patient face-to-face outdoor consultations.

In the hospital setting, the remote care is now being widely used for screening prior to the visit and triage assessment, for the indoor and ICU monitoring and supervising of patients in hospital by off-site experts. This trend is likely to persist to large extent in the post-COVID-19 period, as it provides higher convenience both for clinicians as well as patients.

In the mental healthcare, too, the remote consultation is proving helpful. It is likely that once mental healthcare institutions have developed the capabilities of serving their patients through digital technologies, a blended approach in future would emerge, where e-mental-health solutions cover an increasingly greater part of routine services.

The remote care system in form of HaH is likely to serve further as an adjunct for the gradual adoption of newer and advanced technologies, such as, the use of drones as delivery vehicles for critical supplies, robotics, the widespread 3D-printing of healthcare-related items, and smartphone-enabled monitoring of patients' adherence to treatments.

The healthcare transformation - evolution of HaH

As related to the public health, with the availability of the mobile-enabled technologies, there is an improved operation of surveillance systems and data analysis. The mobile-enabled technologies can be deployed en-masse to monitor quarantined individuals and trace exposed individuals with temporal and geographical correlates. The new tools are likely to move further into the public health domain and support the interconnected and hypercomplex global situations in real-time. On the other hand, the healthcare, in general, is needed to be people centred and integrated. The patient centred services include diagnosis and treatment and other supportive aspects of healthcare, whereas integrated healthcare involves adequate provision and efficient delivery of safe and quality health services. The people-oriented approach, on the other hand, implies planning the healthcare services by assessing the needs and expectations of community and applying them in a methodological and efficient way. The integration of modern technologies including telemedicine in healthcare services will improve the quality of healthcare.

The COVID-19 pandemic has led to realization about the limitations of existing healthcare systems and their capacity to respond to healthcare emergencies including infectious disease epidemics. It has underlined the inadequate health literacy among general population to grasp the healthcare recommendations and their outcomes [6]. It has also served as a reminder for proactive planning and preparedness. In addition, it has highlighted the necessity for technologically oriented solutions for healthcare provision and the need for significant healthcare transformation. On the other hand, it has opened the pathways to evolution and expansion of the concept of HaH incorporating communication technology-based approach as a major step to deliver healthcare at home or closer to home with all necessary steps to safeguard the safety and privacy of the participants. In fact, the healthcare at home (HaH) can be modelled on lines of the hospice care as a multidisciplinary team approach, generally home-based and sometimes providing services through freestanding facilities, in nursing homes, or within hospitals for handling potentially treatable conditions such as pneumonia, heart failure, and alike, with brief hospital stays if necessary (Figure 2).



Figure 2: The development of home-based healthcare and potential spectrum of HaH.

The HaH describes a delivery paradigm where the entirety of the hospital-based inpatient care modality is substituted with intensive at-home treatment approach enabled by digital technologies, multidisciplinary teams, and ancillary services [7]. The potential spectrum of HaH can incorporate the hospice care. But as compared to the latter, apart from providing healthcare services for the terminally ill and elderly in form of hospice care, the HaH can be also useful for all those patients who need intense medical care and treatment but can be managed with help of technological monitoring and remote supervision by healthcare professionals at their homes with possible access to a nearby medical facility or hospital. HaH can make possible for people to receive a variety of medical services in their homes and can satisfactorily deal with various health conditions, as it incorporates therapeutic and nursing care, and medical assistance. In fact, the HaH is being envisaged as an alternate attractive model for accommodating increased demand for inpatient health care and as we prepare for the post-COVID-19 pandemic era, there are evolving salient features of HaH potentially promising to maximize the benefits of transformed health care [8].

The management and delivery of healthcare at home

During the COVID-19 pandemic, there has been a decline in emergency department visits and hospital admission rates in various countries [9]. It seems that in addition to a shift to virtual healthcare, COVID-19 also influenced emergency department visits and hospital admissions unrelated to COVID-19 itself. The studies from both Spain and Italy have shown a reduction in admissions and procedures related to conditions like myocardial infarction and acute coronary syndrome [10,11]. A recent study from Thailand demonstrated that during a national lockdown for COVID-19, there was a significant reduction in daily emergency department visits [12]. Similarly, a study from Melbourne, Australia documented that during times of COVID-19 restrictions there was a significant reduction in ED visits [13]. According to a survey by Canadian Home Care Association, there has been a decline of around 72% in emergency department visits, in turn resulting in the reduction of hospital admission rates [14]. These reductions in outpatient service and admissions underline the need to develop an alternative modality of healthcare for patients still requiring inpatient management for their acute and chronic medical conditions.

The integration of modern technologies like electronic health record (EHR) and telemedicine in healthcare services will save time and resources and provide better healthcare to the users. There are five major technologies which are likely to reform home-based healthcare, and include use of various biosensors, GPS, remote monitoring tools, electronic data and analysis, and telehealth. The e-Prescriptions generated are easy to be transmitted and compatible with the EHR.

In general, the HaH comprises of the following benefits:

With the primary focus of HaH, people get medical support at home rather than spending time in a medical facility. Further, it allows people to stay comfortably at their residential facility rather than at hospitals, having lower cost and various psychological advantages.

Activities of daily living are not altered and supported in-home in usual ways while maintaining a good quality of life for them in the known and perceptive atmosphere.

With the home care provided to patients with chronic health issues such as diabetes and respiratory disease, clinical trials have shown fewer complications and better health outcomes. The personalized and skilled care improves the overall response to the treatment.

With the real-time monitoring with technological equipment, the patients are seen and followed in real-time. Along with the AI and automation, the HaH aims to streamline the processes such as scheduling appointment, data collection, maintaining EHR, e-prescriptions, and scheduling and providing other health-related services as and when needed to improve the overall patient care at home.

The COVID-19 pandemic has amplified interest in HaH in the United States, European countries, and elsewhere as an alternative care model for both COVID-19 and non-COVID-19 patients, who can be remotely managed aided by current regulatory flexibilities [15]. In fact, the HaH is being envisaged as an attractive model for accommodating unprecedented demand for inpatient capacity created by COVID-19. As we prepare for the health care for the post-pandemic era, there are salient issues to be solved to maximize the benefits of HaH -

The HaH models must encompass the provision of healthcare of analogous intensity to hospital inpatient standards, and have a specified geographic catchment area, with properly defined correlates.

As the HaH is supposed to create the acute hospital care at home and to enable health systems to provide intensive care at home for patients with various acute and chronic conditions, this may lead to a remarkable expansion of HaH.

There is a unique opportunity to extend and expand HaH in current times, which can become a new vehicle for integrating non-medical services into healthcare as the patients may require further support due to complexity of their illness.

With the advances in digital technologies and their increased utilization by patients and healthcare providers, there is taking place transformation of the home environment into a preferred healthcare delivery site.

As the health awareness and rising cost of healthcare services may lead to increase in demand of HaH, managing and delivering HaH with technological backup should be affordable and providing quality service.

Further, a regulatory and policy implementation roadmap is required for provision of HaH, which should be accompanied by monitoring tools, such as, public reporting, patient registries, and maintenance of reliable database.

Conclusion

The healthcare solutions for the future

With the COVID-19 pandemic having impact on almost every aspect of human life, the lessons have been learned relating to provision of healthcare. The telemedicine and virtual online consultations have been helpful in dealing with sudden surge and demand for healthcare both outdoor consult as well as emergency visits, and indoor and ICU care. During the COVID-19 and now in post-covid-19 phase the alterations in provision of healthcare and its transformation have been enormous. The conventional healthcare encompassing outdoor consult and hospital-based care is being increasingly replaced by tele- and video- consultations, remote technologically assisted indoor care, and HaH. While the hospital-based care cannot be fully dispensed with, a large proportion of it being increasingly assigned to HaH. The technologically assisted remote healthcare, outdoor as well as indoor, with its availability and acceptability, and associated challenges and benefits, is the new reality of current times.

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Acknowledgement

At the completion of this book, I find myself reflecting on those people who have helped and supported me along the way. The list should begin with my wife, Rashmi a.k.a. Minuji, who has to put up with my erratic working hours both at my office as well as at home and jubilant to a bit depressive moodiness. I love you and wish I could appreciate all things you do on daily basis to make life more comfortable and orderly. I would also like to thank our children - Vibhor and Vindhya, and daughter-in-law, Archana. Looking at them now grown up, facing the world to make their niche is a source of succour and joy.

I would like to mention my thanks to my long-time friend and guide, T. Jacob and his wife, Bina Jacob for their all-present encouragement. I am indebted to my close relatives, Vinita and Manish Gupta for their support accorded in various ways. I am thankful to colleagues, both the doctors as well as the technical and nursing staffs, I am indebted to my colleagues, both the doctors as well as the technical and nursing staffs, at my hospital. Their support came constantly in a sublime way. I must mention my thanks to Dr Hemant Sharma from my Department and Dr Darbari Lal from my Division.

In addition, I want to mention my gratitude to Mr. Williams Robbie, and special thanks to Mr. Michael Simmons, Ms. Lisa, and other the staff members, editors and reviewers from Heighten Science Publications Inc (HSPI), Texas, USA for their background work, editorial help, and encouragement. I am grateful to my friends from the research community to encourage me with nice and factual comments. I am thankful to my various researcher friends at various institutes and universities world over, whom I met during various meetings and conferences and discoursed relating to medical research and developments.

I am thankful to my patients and people whom I have met and meet in daily life to get imbibed and inspired to carry on and find joy in mundane but necessary routine things. I am indebted to my home village and my cities where I have lived, people I have known there, the bygone instances and ever-present memories of innumerable seen and perceived events. Finally, there remain to be thanked umpteenth people, each person a special one, who met by chance and have stayed in touch, making my life beautiful and leaving innumerable cherishable dormant memories.