REVIEW

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Covid-19 And Human Physiological Systems-A Review Based Study

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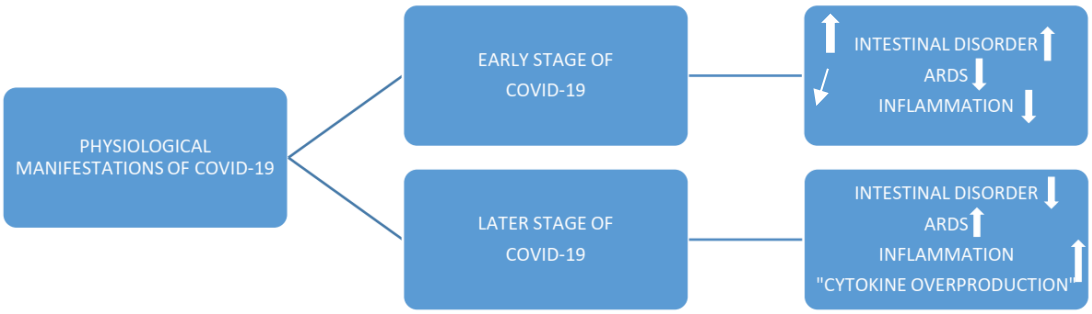
GRAPHICAL ABSTRACT



Schematic Representation of the Physiological Damage in Early and Late Stages of COVID-19 (6)

ABSTRACT

COVID-19 is commonly recognized as a respiratory infection. Effects of COVID-19 are, however, not only restricted to the human respiratory system but all other physiological systems are also prone to COVID-19. The virus can attack many different cells of the body via angiotensin-converting-2 (ACE2) receptors. COVID-19 impact on the human body has been considered as a multi-organ response, causing a range of physiological symptoms. Age-related chronic diseases coupled with a hyperactive inflammatory response can lead to the severity of the infection and death. The risk of physiological complications is higher in comorbidity, weak, and aged patients. Acknowledgment of the various physiological effects of the disease and its complications is fundamental for the proper clinical management of patients. This review aims to provide a detailed perspective on the possible physiological impacts of COVID-19 and adds to the ever-emerging knowledge of human physiology.

Keywords: Contagiousness, Coronavirus, Transmission, Respiratory system, Pandemic

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INTRODUCTION

The novel Coronavirus (widely known as COVID-19) originated from a city in China named Wuhan and later turned into a pandemic, heavily wrecking the physiological and mental health of humans (1, 2). COVID-19 induced by a virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is considered to be originated from a group of bats known as Rhinolophus bats, which lead to myriad ranges of various organ dysfunctions (2). It

has been found to affect more than two hundred million people worldwide and caused 5,316,286 global deaths (3). The above-mention pandemic has been reported to affect the physiological, social, economic, and psychological systems of human beings (4). COVID-19 is transferred to the human body through respiratory droplets in the air or through direct contact with an infected person (5). It primarily affects the respiratory system by attacking the lungs and causing pneumonia (6). The physiological effects of COVID-19 are manifold, which confirms that it is not merely a respiratory infection. Along with the respiratory system, COVID-19 also affects the gastrointestinal, nervous, cardiovascular, and musculoskeletal systems (6, 7, 8, 9).

Inflammation is an obvious outcome of COVID-19 on human physiological systems which may result in an overactive immune response (10,11). Although COVID-19 affects people of all ages, it is deadly and more complicated in older people, especially in those who are already sick and have a compromised immune system (12, 13).

The focus of this paper is to point out the possible effects of COVID-19 on human physiological systems. These effects can get complicated in severely ill patients. Although SARS-CoV-2 directly attacks the pulmonary system, its pathological and inflammatory pathway in other organ systems has not been properly diagnosed and established

Table- 1. A Tabular representation of a range of physiological conditions related to COVID-19 Disease

Cluster No.	**Physiological Manifestations of COVID-19**	**Countries/ Regions**	**Key Findings**	**Reference/s**
1. COVID-19 and human lungs	- COVID-19 and lungs of comorbidity patients	USA	Lung injury Inflammation Hypoxia	(15)
	-COVID-19 and lungs in comparison with influenza	Switzerland, Germany, Massachusetts , and Boston	Perivascular T-cell infiltration and alveolar damage in both COVID-19 and influenza-associated respiratory failure. Endothelial injury and damaged cellular membranes Alveolar capillary micro-thrombi is nine times more prevalent in COVID-19 patients than influenza	Than
	-long-term pulmonary consequences of the COVID-19	Los Angeles, CA	Difficulties in breathing Abnormalities in the diffusion of gasses in the blood.	(19)
	-To study the physiological effects of COVID-19 associated ARDS	Italy	Increased lung weight Increased dead space in the lungs Micro-thrombi and emboli in the pulmonary vascular bed.	(18)
2. COVID-19 and gut	-COVID-19 and gut microbiota	Houston, Texas, and New York	Intestinal damage Enterocyte dysfunction	(6)
	-gut dysbiosis and COVID	Turkey	Altered gut microbiota Increased gut permeability Increased inflammation	(20)
	-Fecal viral activity and alterations in the gut microbiota of patients	Hong Kong	Alterations in fecal microbiome Gut dysbiosis	(21)
	-Alterations of the gut microbiota in COVID-19 patients and H1N1 Influenza	China	A relatively lower abundance of beneficial symbionts The gut microbiota of both patients is different from each other	(22)
3. COVID-19 and human immune system	-COVID-19 and immune responses	Bangladesh, USA	Cytokine storm Increased inflammation Impaired immune response	(24, 12)
4. COVID-19 and brain	-Neurological effects of COVID-19 on humans	USA, Belgium, and Sweden	Damage to CNS Hypoxic injury Encephalopathy Encephalitis Thrombosis	(26, 27, 41)

			Neuroinflammatory responses related to COVID-19 may lead to neurodegenerative problems and neuropsychiatric symptoms Long term neurological complications such as strokes Psychiatric problems such as anxiety, depression, and PTSD	
	-To study the neurological sequelae of COVID-19	US, Mexico, and Canada	In the central nervous system: Viral entry into the brain Adverse immune responses Respiratory stress In the peripheral nervous system: Chemosensory dysfunction	(5)
	-To study how COVID-19 can damage the brain	United Kingdom	Damage to brain blood supply in most patients can lead to stroke and hemorrhage The altered mental state of patients leads to confusion and prolonged unconsciousness Encephalitis is rare Less common complications include PNS damage, which can cause anxiety, PTSD, and loss of smell	(28)
	-To study brain injury in comorbidity patients and neurological effects of severe COVID-19 infection	USA and Italy	Brain injury in comorbidity patients due to: Encephalitis Ischemia Oxidative stress	(8, 15)
	-To study the neurological involvement in COVID-19	USA	Cytokine storm can lead to neurological injury Apoptosis and necrosis in brain parenchyma in the medial temporal lobe Cerebral hemorrhage PNS damage Loss of taste and smell	(40)
	-Neurological and neuropsychiatric complications	UK	Altered mental state Encephalopathy Encephalitis	(29)
5. COVID-19 and Cardiac System	-Impact of COVID-19 on the heart in comorbidity patients	USA	Plaque rupture Myocardial injury Arrhythmia Coronary thrombosis Venous thromboembolism Heart injury Ischemia	(15)
	- COVID-19 and heart	Italy, India	Deterioration of previously existing cardiovascular disorders Inflammatory heart disease Conduction disturbances Disseminated intravascular coagulation Myocardial injury Pre-existing cardiovascular diseases increase the risk for COVID-19 infection Cardiovascular complications in comorbidity patients	(7, 34, 35)
6. COVID-19 and liver	-To study the effects of COVID-19 on liver function and hepatic injury	India, Singapore	COVID-19 patients indicate mild hepatic injury Common hepatic injury is related to low albumin levels in the blood More common in patients who require mechanical ventilation and intensive care and	(36, 37)
7. COVID -19 and musculoskeletal system	-To study t impact on the musculoskeletal consequences	New York	Musculoskeletal dysfunction In skeletal muscle: Muscle pain, muscular atrophy, fatigue, and weakness In joints and bones: Joint pain and immense loss in bone minerals	(9)

8. COVID-19 and mental health	-To study the effects of COVID-19 on mental health	Italy, Brazil, and Paraguay	Stress, depressive symptoms, anxiety, denial, insomnia, fear, and anger may Emerging mental health issues may evolve into long-lasting health problems, stigma, and isolation.	(1)
	-COVID-19 and mental health	Ohio	Health care workers, people with pre-existing medical or psychological problems, those who contract it, and also those who are in quarantine are at an increased risk for adverse psychological problems such as irritability, insomnia, fear, confusion, frustration, boredom, anger, stigma, stress, mood swings and depression Suicidal thoughts may emerge	(33, 42, 43, 46)
	- COVID-19 and mental health of females	UK and Germany	Changes in hormone levels increase emotional sensitivity to pre-existing stressful situations related to COVID-19	(45)
9. Age-related impact of COVID-19	-COVID-19 and age-linked comorbidities	USA	Number of fatalities according to age; Age >85 years old: 10-27% (the highest fatality rate) Age 65-84 years old: 3-11% Age 55-64 years old: 1-3% Age 20-54 years old: <1% Age 19 years old: No fatalities Age and age-related chronic diseases lead to increased inflammation and mitochondrial dysfunction Inflammation and mitochondrial dysfunction can lead to weakened immune response and increased severity of COVID-19	(12, 13)
10. COVID-19 and comorbidity patients	-COVID-19 and comorbidity patients	India, Italy	People with pre-condition of hypertension, diabetes, and cardiovascular diseases are more prone and may lead to heart failure.	(34, 35)
	-Impact of COVID-19 on brain and heart of patients in comorbidity	USA	In comorbidity patients (i.e. diabetic patients): Severe complications High mortality rate High ICU admissions Inflammatory responses Hepatic, Cardiac, and renal coagulopathy	(15)
	-To study the effects of COVID-19 on pre-existing cardiovascular disorders	Italy	Deterioration of pre-existing medical conditions	(7)

EFFECTS ON THE LUNGS (Initial and Progressive Phases of COVID-19)

Epidemiological studies marked various phases indicating the COVID-19 development. COVID-19 symptoms tend to develop during the period of 2 to 14 days. However, these symptoms were not diagnosed as identical in every infected person. COVID-19 Symptoms range from mild (*i.e.,* flu or cold-like condition) to severe (*i.e.,* fever, cough, and breathing difficulties). Other symptoms include digestive issues and/or loose stools (14). Lung injury, inflammation, and hypoxia are predominant respiratory symptoms of COVID-19 (15). When compared with influenza patients, the COVID-19 patients indicated the state of angiogenesis and the presence of microthrombi in the alveolar capillaries (16). COVID-19 virus invades lung cells by attaching to the angiotensin-converting enzyme 2 (ACE2) receptors. Following the attachment, ACE2 activity decreases in the cells which, on the other hand, increases ACE1 activity. The increase in ACE1 activity produces more angiotensin 2 which is a naturally occurring vasoconstrictor peptide hormone recognized for raising blood pressure by triggering aldosterone production. High levels of angiotensin-2, provide attachment sites for SARS-COV-2 in the human lungs, which may thus lead to the COVID-19 severity. ACE2 normally reduces the levels of angiotensin 2 in the body by consuming it. As COVID-19 downregulates ACE2, build-up of angiotensin-2 occurs in the body, which may result in the development of acute respiratory distress syndrome (ARDS) and cardiac injury in human beings (Figure 1) (17).

COVID-19 along with the ARDS may injure lungs in the same pattern as the classical ARDS. The

manifestations of classical ARDS include increased lung weight and decreased compliance which can get complicated by increased dead space and thrombi in the lungs (18). It has been observed that the majority of survivors may live their normal lives. However, persistent and prolonged pulmonary abnormalities like residual ventilation and irregular diffusion of blood gasses have been observed in a significant number of survivors (19).

EFFECTS ON THE GUT

The earliest symptoms of the disease involve a major effect on the gut and fecal microbiomes (6, 20, 21, 22). During the initial phases, COVID-19 patients are marked with high levels of viral load were faced with gastrointestinal problems (Figure 6). Viral attachment with Angiotensin-Converting Enzyme 2 (ACE2) receptors is followed by the infection of gastrointestinal cells with SARS-CoV-2 which may lead to inflammation and diarrhea (6). Prolonged and persistent exposure to the virus in the guts of the survivors even after the pulmonary removal of the virus (21).

There are two different possible routes of viral infection in the gastrointestinal tract (GIT):

1. The ACE2 receptors are exceedingly expressed in the epithelial cells of the GIT which leads to the receptor-mediated entrance of the virus into the cells of the host (23).
2. Pulmonary infection of COVID-19 induces an inflammatory immune response which leads to viral translocation from the lungs to the circulatory system. Once in the circulatory system, the virus stimulates the activation of cytokines resulting in an exaggerated immune response and hence, further augments the inflammation. In response to this, gut permeability may increase which could result in the alteration of the gut microbiota. The change in gut microbiota known as gut dysbiosis leads to the transfer of infectious agents and toxic substances to the circulation resulting in the development of severity in COVID-19 and multiple organ failure. Other physiological conditions such as pre-existing medical disorders and increased age contribute to the severity of the disease (Fig. 2) (20, 23).

EFFECTS ON THE IMMUNE SYSTEM

The immune system in human beings is meant for the protection against various xenobiotics and infections. The early phase of COVID-19 is characterized by the initiation of innate cytokine response. The later phase of COVID-19 conversely can be characterized by 'cytokine storm' and inflammation (24) (Figure 5). Cytokines are, however, small protein molecules secreted by the cells of the immune system in the blood or directly into the tissues. They regulate different functions of the immune system by looking for target immune cells to bind and interact with, to activate specific immune responses (Figure 5). The immune system of COVID-19 patients may produce both anti-inflammatory and pro-inflammatory cytokines. Lung damage, dysfunction, and decreased lung capacity can occur as a result of an uncontrolled or overactive immune response (17).

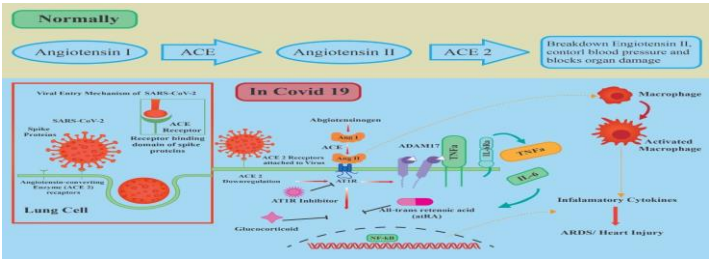

Figure. 1. Schematic Representation of the Role of ACE2 Receptors and Angiotensin 2 in COVID-19 (17).

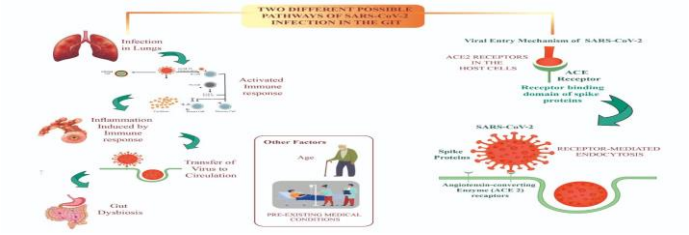

Figure. 2. Schematic Description of the Development of Secondary COVID-19 Infection Along the Gut and Lung Pathway (20, 23).

Cytokine storm is a serious disorder characterized by cytokine overproduction, over-activation of immune cells, systemic inflammation, and multiple organ damage (25). A hyperactive immune response has an obvious physiological impact in COVID-19 patients (26). However, people having strong immune systems are less prone to serious COVID-19 infection (12).

EFFECTS ON THE NERVOUS SYSTEM

COVID-19 can cause a range of neurological symptoms for instance loss of smell, headache, unconsciousness, and stroke (27). Such symptoms can be the result of COVID-19 induced immune responses, respiratory stress in the Central Nervous System (CNS), and chemosensory dysfunction in the Peripheral Nervous System (PNS) (5). Along with psychosis in a few patients, COVID-19 has also been observed to cause mental disturbances (31% patients), strokes, and hemorrhages (62% patients). Some people with COVID-19, however, also experience confusion, agitation, and disorientation during hospitalization (28, 29). There are three different possible scenarios for the damages in Central Nervous System (CNS) (5, 26).

The manifestation of damages in the Peripheral Nervous System (PNS) is characterized by chemosensory dysfunction. The pathway of PNS damage may involve the entry of a virus into the brain cells following the same pathways as CNS. This triggers an inflammatory immune response in the PNS leading to anosmia and ageusia (5).

The pathway for nervous system infection by SARS-CoV-2 may involve three different pathways *i.e.*, olfactory pathway, ACE2 receptors, and blood circulation pathway.

Olfactory Pathway: SARS-CoV-2 might vitiate the CNS which may initiate from the olfactory bulb, then move to the brain's inner parts such as the brainstem and thalamus with the help of trans-synaptic transfer. From there on, this virus might target the respiratory center of the brain. It is the common pathway for both CNS and PNS as the virus may also affect the chemosensory function of the brain (30, 5).

1. **ACE2 Receptors:** SARS-CoV-2 recognizes the ACE2 receptors present on the surface of neurons, neuroglia, and capillary epithelium. The ACE2 receptors express themselves on these cells which makes them susceptible to SARS-CoV-2 attack. Through these cellular receptors, the virus may damage the capillary endothelium and gain access to the brain (31). This pathway involves CNS only.
2. **Cerebral Blood Circulation Pathway**
    a. The viruses that affect the CNS do so by directly affecting the nerve endings found in the tissues or by targeting the cells of the circulatory system. This would further result in the transfer of the virus through the blood-brain barrier into the CNS (32). SARS-CoV-2 and cytokines could target the endothelial cells which can result in inflammation and damage to the blood-brain barrier. This pathway explains the CNS invasion by the virus (26) (Figure 4). As the neurological symptoms become more serious with strokes, hemorrhages, and memory loss, the main question is, why is the brain impacted at all? Moreover, whether the neurological symptoms are the result of a hyperactive immune system or the virus directly invades the cells of the brain is still not obvious and requires further research (28).

EFFECTS ON MENTAL HEALTH

This pandemic has been reported to cause mental and health issues among humans *i.e.* stress, anxiety, depressive symptoms, denial, insomnia, and anger. These developing mental health issues may result in long-lasting human health issues like isolation and stigma (1). Some people may be more exposed than others to the psychological and social effects of a pandemic. Quarantine, loss of freedom, boredom, and self-isolation create a negative impact on mental health (42). People with weak immune response, living or caring in congested places, and with pre-existing medical or psychological issues are more prone and vulnerable to developing the disease health-care workers are particularly more susceptible to the psychological issues and emotional stress in the pandemic since they are regularly exposed to the virus, work for longer hours and care for the sick (33,43). Due to the rapid spread of COVID-19, emigrants and immigrants have been reported to face hostility, stigmatization, and discrimination (43). The mental health of females is considered more susceptible and vulnerable to stress as compared to males. It may be due to the fluctuations in ovarian hormone levels which change the emotional sensitivity to various stress stimuli (45). It is analyzed that younger age groups have a high tendency of stimulation against surrounding stressors of COVID-19 (44). COVID-19 pandemic is also the major contributor to domestic violence, loneliness, and child abuse. It may be the increase in isolation during lockdowns due to which closeness of abusers and victims has taken place and escape is not possible.

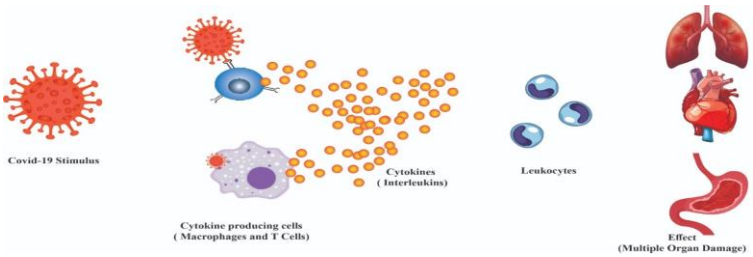

Figure. 3. Representation of the Role of Cytokines in Immune Response (17, 25).

THREE DIFFERENT POSSIBLE SCENARIOS OF DAMAGES IN CENTRAL NERVOUS	**1.** SARS-CoV-2 may enter the CNS through nasal passageways, gain access to the olfactory bulb, and mucosa as well as the cerebral circulation. The ACE2 receptors found in endothelial cells and blood vessels are identified by the virus which can further lead to apoptosis of brain cells. Consequently, cerebral edema occurs which causes the compression of the brain stem. Moreover, entry of the virus and recognition of ACE2 receptors on the endothelial brain cells can also damage the blood-brain barrier. This is because the virus is transported across the blood vessel into the neurons
	2. COVID-19 also causes an overactive immune response in the body due to the cytokine storm. This can result in apoptosis of brain cells which ultimately cause Acute Necrotizing Encephalopathy (ANE) and hemorrhage.
	3. The third plausible scenario of CNS damage involves the respiratory stress caused by the depletion of oxygen in the lungs. This hypoxic condition can result in brain cells injury.

Figure. 4. Three different possible scenarios of damages in the central nervous system (CNS) (5, 26).

Fear and stress are major contributing factors in the widespread dissemination of mental health conditions. During this pandemic, anxiety and depression show their peak increase in their symptoms with an increase in a low mood, limited interest, and a decrease in energy in daily activities (46).

EFFECTS ON THE HEART

The cardiac physiological symptoms in COVID-19 sufferers may include hypoxia, myocardial injury, plaque rupture, arrhythmia, coronary thrombosis, venous thromboembolism, dispersed intravascular coagulation, and inflammation (7, 15). Several patients with myocardial damage can develop serious cardiovascular issues which may include heart failure (34). SARS-CoV-2 may cause myocardial injury in three possible ways,

1. The virus may directly attack cardiac cells by attaching to ACE2 receptors.
2. Arterial hypotension leading to oxygen dysregulation in the heart may also be the reason for myocardial injury.
3. Cytokine storms can lead to an impaired immune response which may eventually result in myocardial injury (Figure 5) (15, 25, 35).

A bidirectional association has been found between COVID-19 and cardiovascular diseases (CVD). On one hand, people with pre-existing CVD are supposed to be at an increased risk of becoming infected with COVID-19. Thus, are considered more likely to acquire a severe form of the disease. On the other hand, some people infected with COVID-19 develop cardiovascular symptoms in addition to other complications associated with the COVID-19 (35).

LIVER DYSFUNCTION AND INJURY

Liver injury is prominent in severe disease groups of COVID-19 (36, 37). The Insufficient level of albumin in the blood and cirrhosis are the main contributors of developing severity in COVID -19. This is considered to be due to immune dysregulation which may be traced in abnormal liver function tests i.e., alanine transferase (ALT) and aspartate transferase (AST).

The mechanism of the COVID-19 effect on liver dysfunction may be multifactorial but still is not fully understood. ACE2 is the host cell receptor of SARS-CoV-2. Entry of SARS-CoV-2 involves transmembrane serine protease 2 (TMPRSS2). Minimal or no Expression of ACE2 messenger RNA (mRNA) has been reported in hepatocytes. The expressions of TMPRSS2 mRNA were found in hepatocytes. Hepatocytes were reported to contain no ACE2 protein. All these findings have suggested that SARS-CoV-2 has not been found to directly cause the cytopathic damage of hepatocytes. Hepatocellular Carcinoma cell line Huh-7 has been found to show SARS-CoV-2 replication (26). The cytoplasm of

hepatocytes has been found to contain SARS-CoV-2 particles without any membrane-bound vesicles (49). Factors like liver enzymes, liver steatosis, and liver fibrosis have been found as contributing factors in developing the severity of COVID-19 (49, 50, 51). However, no significant change in the transaminases and bilirubin levels of COVID-19 diagnosed patients has been observed (52). Patients with cirrhosis have been reported to be at high risk of mortality. This risk may occur through multiple converging pathways, which may include acute hepatic decompensation, cirrhosis-associated immune dysfunction, and systemic inflammatory response. Cirrhosis-associated immune dysfunction may also lead to defective immune responses followed by the future SARS-CoV-2 vaccination (53). A decline in liver functioning may further quadruple the risk of developing severe corona infection. Patients thus having chronic hepatic diseases and/or cirrhosis are considered more susceptible to the COVID-19 severity (54).

EFFECTS ON THE MUSCULOSKELETAL SYSTEM

The coronavirus infection has been found to cause weakness and fatigue in the skeletal muscle. In the bones and joints, it causes loss of bone tissue and cartilage. However, it is not known whether these symptoms are the result of systemic inflammation alone or the virus directly infects the cells of the musculoskeletal system (9). During the first four days of infection, a rapid twenty percent loss in the body occurs. The direct effects of COVID-19 mean the process of active infection of a virus on a patient's musculoskeletal system. First, COVID-19 hits the respiratory tract, especially the alveoli epithelium which accesses the virus to the bloodstream, the coronavirus disseminates throughout the body. This damages the other systems such as myalgias, sarcopenia, muscle loss, Cachexia, myasthenias, and fatigue. The indirect effect on the musculoskeletal system has been found more prevalent in those patients who face prolonged exposure to inactivity such as in ICU and because of strict lockdowns. During the lockdown, people are limited to exercise at home. This creates a negative impact on muscles due to unused muscle allocated energy. This may be reallocating the metabolic substrates in the liver which leads to an increase in obesity (anthropogenic lipoprotein production) and atherosclerosis (increasing the risk of lipids collecting in blood vessels). Most ICU patients require the use of invasive ventilation to maintain a constant airflow which may be the cause of bone and muscle frailty (55).

The inflammatory response is produced as a result of the primary stage of pulmonary infection, which causes an integral impact on the human musculoskeletal system. Various types of musculoskeletal cells show the ACE2 and TMPRSS2 genes, which are necessary for direct viral infection. But the way of these genes' infection is still unclear (9). Myalgia means muscle pain and aches. Primarily, immune-mediated mechanism theory is considered the most extensively accepted theory of muscle damage in corona patients. Secondly, inflammatory response with cytokine storming mechanism and immune cells activation was also accepted for muscle damage. These suggested mechanisms cause immune complex deposition, myotoxic cytokine release, and injury secondary to homology between human muscle cells and viral antigens.

Myositis (inflammation of muscles), Rhabdomyolysis (a complication of myositis involving myonecrosis and myoglobinuria), Virus-induced arthritis Diaphragm muscle dysfunction were also reported in COVID-19 patients (56). Acute necrotizing hemorrhagic encephalopathy, also present in patients with COVID-19, is associated with inflammation.

This increases the vascular permeability causing edema, necrosis, and petechial hemorrhage (57).

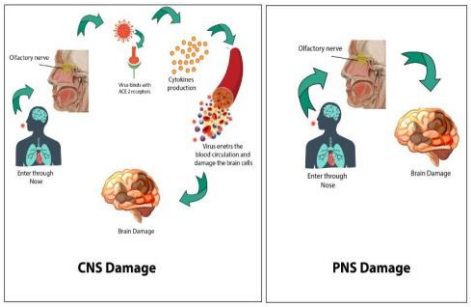

Figure. 5. Schematic Representation of the Pathway of Nervous System Damage in COVID-19 (5, 26, 30, 31).

AGE-RELATED EFFECTS OF COVID-19

In the case of patients having age-related chronic diseases, increased inflammation and mitochondrial dysfunction occur which leads to a weakened immune response causing a severe form of COVID-19 (12).

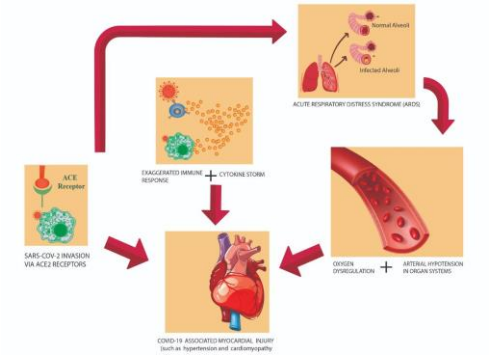

Figure.6. A schematic representation of the possible causes of myocardial injury in COVID-19 (15, 25, 35)

Older people also have decreased diversity of gut microbiota which could be the reason for the severe form of infection. Center for disease control and prevention (CDC) revealed through a published report that the highest mortality rate was found in people as aged as eighty-five (85) or older and no casualties were reported among the individuals aged as 19 or younger (13). Adolescents and children were found affected by aggressive behavior and depression due to COVID-19 lockdown measures (58). High mortality risks in older adults have been reported due to the increased level of anxiety, fear of death, optimism, and social isolation (59). Social vulnerabilities such as low income and unemployment also are the major factors of creating mental issues in many developing countries with financially downtrodden situations (60).

EFFECTS ON COMORBIDITY PATIENTS

COVID-19 may appear as asymptomatic, or with mild and severe pneumonia-like symptoms. It was found that patients diagnosed as suffering from coronavirus were mostly reported with a pre-condition of cardiovascular diseases (CVD), diabetes, chronic obstructive pulmonary disease (COPD), hypertension, HIV, malignancies, and some other diseases which may also tend to develop some life-threatening situations. ACE-2 receptors are responsible for the entry of SARS-COV-19 into the host cell. Certain pro-protein convertases are released due to the expression of ACE-2 receptors which may further enhance the entry of viruses into host cells. These comorbidities may further lead these coronavirus patients into a vicious and infectious cycle. In addition, they are also substantially associated with a significant level of mortality and morbidity (61). Hypertension, renal disease, cancer, HIV, dementia, chronic pulmonary disease, and diabetes are the predominant comorbidities that show high mortality rates in patients affected by COVID-19 (62). In addition, it was found that populations with pre-existing diseases like cardiovascular and cerebrovascular, renal infections, and hypertension are considered more prone to coming under the attack of coronavirus.

This article further provides ample evidence to indicate the impact of certain comorbidities on COVID-19 severity. Comorbidities including diabetes and other age-linked diseases may lead to increased inflammation and abnormal mitochondrial function which can further weaken the immune response resulting in COVID-19 severity (12). A comparative hospital-based study on non-diabetic and diabetic patients having COVID-19 has shown high shifting ratios of diabetic patients into ICU *i.e.* Intensive Care Unit and/or high mortality ratio. This can further be safely concluded that COVID-19 patients with pre-condition of diabetes mellitus have shown severe inflammatory immune responses as compared to non-diabetic patients (39).

CONCLUSION

During its course, SARS-COV-19 has been found to target many vital organs which may cause life-threatening physiological complications (26). Being a respiratory infection, COVID-19 has been found to mainly cause pneumonia. Gut dysbiosis is the major effect on the gastrointestinal system which also occurs in the early phase of the disease. Neurological complications include strokes, hemorrhages, and impaired consciousness. Cardiovascular manifestations are observed in severely ill patients and the situation of people with pre-existing CVD can get worse during COVID-19. Low levels of albumin in blood and weakness in muscles and joints are also observed. Hyperactive immune system and cytokine storm syndrome may quadruple the severity. Moreover, the negative influences on the economy, physical and mental human health along with the social interactions are considered as damaging globally. A global comprehensive response regarding a focus on COVID-19 patients' mental health has also been considered as an essential factor and should be encouraged worldwide. Moreover, COVID-19 related news dispensed through social media and other platforms must closely be monitored and other community relief programs regarding human mental health must be encouraged worldwide.

Some common diseases like hypertension, coronary artery, and diabetes-like diseases are considered as the most common comorbidities among COVID-19 patients. People who are weak, aged, and sick are considered most prone to develop severe complications and may require intensive care and mechanical ventilation. It should be noted that the majority of people recover from the disease and continue with their normal lives but some people may have long-term effects on their health.

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