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Extrapulmonary Manifestations of COVID-19 in Mild/Severe Patients

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Abstract
The coronavirus disease 2019 (COVID-19) caused the outbreak of viral pneumonia in Wuhan, China, in December 2019. It is principally identified with respiratory disease and pulmonary manifestations. However, based on various reports, COVID-19 infection not only affects the respiratory system but also infects other organs. Cardiac manifestations, gastrointestinal complications, liver dysfunction, musculoskeletal disorders, ocular findings, and hematological manifestations are among the published extrapulmonary clinical manifestations. Lack of awareness and attention to these extrapulmonary features might result in misdiagnosis, delayed diagnosis, incorrect treatment, and eventually an increase in the spread of the virus by unidentified individuals to others in the community. Therefore, the current study comprehensively reviews and discusses the extrapulmonary manifestations of COVID-19 in mild or severe patients.
Keywords: COVID-19, SARS-CoV-2, Extrapulmonary manifestations, Cardiac manifestations, Gastrointestinal manifestations

Background

Coronavirus disease 2019 (COVID-19) is an airborne disease transmitted primarily through respiratory droplets containing the virus.[1,2] The causative pathogenic agent is an enveloped, non-segmented, positive single-stranded RNA virus, β-coronavirus, which is called the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[3] The mean incubation period ranged from 5.6 to 6.7 days.[4] The mechanism of cellular entry by SARS-CoV-2 is through the virus spike protein (S-protein) binding to receptors named angiotensin-converting enzyme 2 (ACE2). ACE2 is the primary host cell receptor found in almost all organs, including the lung, brain, small intestine, colon, oral mucosa and nasopharynx, kidneys, stomach, smooth muscle cells, bone marrow, spleen, and liver.[5] The most prevalent clinical manifestations of SARS-CoV-2 are fever, cough, and fatigue, and the least common manifestations are conjunctival congestion/conjunctivitis, gastrointestinal symptoms, anosmia, and ageusia.[6-8] Furthermore, coagulation disorders, septic shock, and multiple organ dysfunction are associated with prolonged intensive care unit (ICU) stay and increased mortality.[9] The severity of COVID-19 depends on the underlying disease, age, and gender. The elderly's immune system response to formerly exposed pathogens is more preserved compared to those that have never been exposed. In contrast, in children, a considerable number of naive T cells are prepared to encounter new pathogens which might be the reason for milder COVID-19 status and lower mortality rates among children.[10] Moreover, risk factors such as smoking, co-morbidities, and obesity are less common in children.[11] The estimated case fatality rate of COVID-19 in the general population, hospitalized patients, patients admitted to ICU, and patients older than 50 years was reported to be 1%, 13%, 37%, and 19%, respectively. It has been reported that for every 10% increase in vaccination coverage, the COVID-19 mortality rate could be reduced by 7.6%.[12] Contrary to much knowledge about pulmonary manifestations, there is inadequate evidence about extrapulmonary features in mild or severe COVID-19 patients. This article comprehensively mentioned the extrapulmonary manifestations of COVID-19 infection.

Cardiac Manifestations

COVID-19 patients can develop heart failure at different stages of the disease. New or preexisting heart failure has created a complex situation that needs more attention for better management and prognosis. In a growing number of reports, COVID-19 patients have been

hospitalized for lung-related symptoms but died from heart failure. Therefore, cardiac abnormalities should be assessed in patients recovered from COVID-19. ACE2 receptor is highly expressed in the heart, making the heart a significant target for SARS-CoV-2 infection and injury.[13,14] Cardiovascular indications are not the same as the patient infected with MERS-CoV who was found to have acute heart failure secondary to myocarditis confirmed by cardiac MRI.[15] Multiple mechanisms have been suggested for cardiac damage as follows[16-21]:

(A) Many studies have shown that the connection between SARS-CoV-2 and myocardial injury can lead to a heart attack because of the direct effect of the virus, as SARS-CoV-2 enters myocardial cells directly by binding to the ACE2 receptor.

(B) Inflammatory cytokines can be produced following the entrance of the virus to the human cells. The overexpression of inflammatory mediators (including TNF-α, IL-1β, and IL-6) can contribute to cytokine storm, as have been observed among severe COVID-19 patients. The heart muscle can also be damaged, which is classified as myocarditis or weakening of heart muscle function and may manifest as dilated cardiomyopathy and/or heart failure.

(C) Myocardium is a highly oxygen-dependent tissue. In patients with acute symptoms of SARS-CoV-2 infection, the infection may impair lung function. The development of acute myocardial injury in COVID-19 patients may be associated with an imbalance between myocardial oxygen supply and demand. The low oxygenation of tissues can lead to hypoxic injury to the heart and many other organs.

(D) The association between acute infections and myocardial infarction has already been demonstrated, and COVID-19 patients are not exempt from this issue. Atherosclerotic plaque instability increases as intra-plaque inflammatory activity increases, and a systemic prothrombotic and procoagulant state after plaque rupture increases the risk of coronary thrombosis. Furthermore, a high stress level in COVID-19 patients can exacerbate underlying cardiac risk factors, including atherosclerotic plaque rupture.

(E) Irregular heart rhythm is one of the symptoms in COVID-19 patients, which is the consequence of illness, not the direct effect of the virus, but has the potential for creating other heart problems such as arrhythmias.

(F) There is a relationship between coagulation dysfunction and cardiac injury in COVID-19 patients, and it can disrupt blood flow.

G) Cardiac toxicity may occur in a COVID-19 patient with severe multi-organ dysfunction who is taking medication for therapies.

In hospitalized patients, the prevalence of cardiac injury has been reported to be between 7% and 28%.[22] Some risk factors and SARS-CoV-2 can cause serious cardiovascular complications, and preexisting cardiovascular disease (CVD) is associated with a more severe COVID-19 course. Several studies have demonstrated similar findings with higher mortality risk in patients with prior CVD.[22] Cardiovascular complications are common and result from various mechanisms. Implementing quarantine to reduce the spread of the COVID-19 pandemic affects cardiovascular risk factors, leading to an increase in cardiovascular risk burden, which is mainly associated with unhealthy lifestyle and anxiety.[23]

Pathogenic Considerations

Acute Myocardial Injury

It is still unclear whether the acute injury is due to a primary viral infection or a secondary cause of lung disease or systemic inflammation.[24] Cytokine storms may also cause myocardial injury in patients with COVID-19.[25] The high level of ACE2 expression in cardiomyocytes probably indicated that SARS-CoV-2 has a direct role in cardiac injury. Recently, SARS-CoV-2 was identified by real-time PCR in some patients with heart problems.[26] Some studies demonstrate that acute myocardial injury can increase the disease burden, need for ICU care, and risk of death. Moreover, patients with acute myocardial injury showed higher levels of C-reactive protein (CRP) and PCT and a greater pulmonary lesion ratio.[27] Viral damage to infected myocardial cells via ACE2 receptors found on these cells may lead to an inflammatory storm and/or an imbalance of oxygen supply caused by acute respiratory distress syndrome. Due to the lack of information on this topic, more in vitro and in vivo studies are needed.[22,28]

Arrhythmias

Arrhythmia is a problem with the rate or rhythm of the heartbeat, and both tachycardia and bradycardia arrhythmias are known to happen in COVID-19. Reports from China suggest that patients with COVID-19 have a 16.7% incidence of cardiac arrhythmias. A higher rate of arrhythmia (44%) was observed in patients with COVID-19 admitted to ICU.[29] Cardiac arrest and arrhythmias may result from systemic illness, not a direct effect of COVID-19 infection.[30]

Acute Coronary Syndrome

Acute coronary syndrome (ACS) describes as a situation in which the blood flow to the heart decreases. SARS-CoV-2 infection in England has been detected in 4% of ACS patients. A meta-analysis study showed that 1.6% of patients with COVID-19 had ACS.[31] ACS is characterized by elevated cardiac troponin and is usually related to atherosclerotic plaque disruption (rupture or erosion), a cytokine storm, and a hyperinflammatory condition.[32] The relationship between COVID-19 and ACS can be explained in two ways. First, the patient becomes infected with SARS-CoV-2 when ACS is present in the background; therefore, COVID-19 infection occurs

later, and ACS is a consequence of atherothrombosis. Second, after two weeks of COVID-19 infection, ACS occurs due to vasculitis and hypercoagulation.[33] In a previous study, COVID-19 ACS patients were generally older black Asian and of minority ethnicity and showed clinical characteristics such as higher cardiac troponin, pulmonary edema, cardiogenic shock, and poor left ventricular systolic function in comparison with non-COVID-19 ACS patients.[32]

Arterial and Venous Thromboembolism

Venous thromboembolism (VTE) and arterial thrombosis (ATE) are associated with coronavirus disease. A meta-analysis study has shown that the frequency of COVID-19-related VTE was 14.7%, and the frequency rate of ATE was 3.9%. In addition, it concluded that patients admitted to the ICU for severe COVID-19 had a higher risk of VTE.[31] During COVID-19 infection, different factors, such as elevated D-dimer and acute inflammation due to severe infection, can lead to the activation of the coagulation cascade and inhibition of the fibrinolytic reaction, thereby causing thrombosis.[34,35] A meta-analysis study suggested that the pooled mortality rate among patients with thromboembolism was 23% and it was 13% among patients without thromboembolism.[36] Anticoagulant thromboprophylaxis is recommended if there are no contraindications.[37]

Gastrointestinal Manifestations

COVID-19 has many gastrointestinal manifestations that can occur even without respiratory complications. COVID-19 patients also frequently show gastrointestinal symptoms, including anorexia, diarrhea, nausea, vomiting, and abdominal pain.[38,39] The SARS-CoV-2 virus can be isolated from the faeces of infected people up to 10 days after resolving symptoms and even after the virus clearance from the respiratory system.[40] Therefore, there is concern about the chance of fecal-oral transmission of the virus. Hence, its diagnosis is possible using stool samples, which reduces the false negative rate if the nasopharynx is negative, suggesting that some inflammatory bowel diseases may increase the risk or severity of COVID-19.[41] Although respiratory symptoms are the main manifestation of COVID-19, many patients also have gastrointestinal symptoms simultaneously, and some patients even show gastrointestinal symptoms without respiratory symptoms.[42] During the COVID-19 quarantine, the frequency of several upper gastrointestinal symptoms increased, which is mainly linked to the level of anxiety.[43] In a study of 206 patients with moderate SARS-CoV-2 infection, 23% of patients had only gastrointestinal symptoms, 34% had both gastrointestinal and respiratory symptoms, and 43% had respiratory symptoms alone. Anorexia, diarrhea, vomiting, and abdominal pain were reported in 49.5%, 32.5%, 11.7%, and 4.4% of the patients, respectively.[44] In another study conducted in China on 204 patients with COVID-19 in three major hospitals, 103 patients had gastrointestinal symptoms as the main problem)including anorexia, diarrhea, vomiting, and abdominal pain, respectively) and 6 patients had gastrointestinal symptoms without respiratory symptoms.[45] Patients with gastrointestinal symptoms had higher PT and AST, antimicrobial therapy, and lower monocyte counts. It was also observed that 69.2% of people had moderate disease, and 100% of people with severe disease had anorexia during the visit. They also found that gastrointestinal symptoms increased with the increasing severity of the disease, but there was no significant difference in discharge or mortality among them. These reports indicate the importance of gastrointestinal symptoms in the recovery process of COVID-19, especially in mild patients. Patients with gastrointestinal symptoms and mild COVID-19 facilitate the spread of the virus in communities and appear to be the major cause of the pandemic.[45] In general, the SARS-CoV-2 S protein interacts with the ACE2 receptor on the surface of cells to enter the host. ACE2 is also highly expressed in the gastrointestinal tract in the basal layer of squamous epithelium, smooth muscles of intestinal and gastric mucosa, duodenal enterocytes, jejunum, and terminal ileum of the colon.[41,46] Therefore, it is also known as a target organ for the virus. A study by Baryah et al showed an increase in the expression of ACE2 in IBD patients, which suggests that people with IBD are more susceptible to COVID-19 and may have more intense manifestations if contaminated.[41] It was also stated that patients with gastrointestinal symptoms rarely had underlying gastrointestinal diseases. Another study found that approximately 10% of patients with nausea and vomiting present 1 to 2 days before shortness of breath and fever.[47] The liver is also a target organ for the virus, where ACE2 is expressed primarily in cholangiocytes (bile duct cells) (59.7%) and hepatocytes (2.6%).[29,46] Various studies have reported liver enzyme disorders in 50% of patients with COVID-19. In one study, 41% of COVID-19 patients had abnormalities in liver enzymes. Even in mild cases of COVID-19, the prevalence of liver failure was reported to be 23.5%. These abnormalities are also associated with disease severity and test results such as higher A-aDO2, higher FER, lower albumin, and decreased circulating CD4 + T cells, and B lymphocytes. Abnormalities of liver aminotransferase are related to disease severity and higher radiological score, especially in this research, in which 55.6% of patients presented with severe (acute) disease and 23% with non-acute (mild) disease along with increased liver enzymes. Nine severe patients, including 5 with acute respiratory disease syndrome (ARDS), 2 with sepsis, 1 with acute kidney injury, and 1 with uremia, were admitted to the ICU, among whom 7 (77.8%) cases presented with liver enzyme

abnormality. Mortality occurred in 3 (4.7%) patients with liver enzyme abnormalities and 1 (1.1%) patient with normal liver enzymes. The mean length of hospital stay among patients with abnormal and normal liver enzymes was 19 days and 15 days, respectively.[48] In addition, a study reported that gamma glutamyl transferase was found in 30 of 56 patients with COVID-19.[29] Additionally, the autopsy of a patient with COVID-19 who presented with multiple cerebral infarctions showed a grey liver and a swollen gallbladder. However, there was no sign of liver failure.[49] Nevertheless, another study on autopsies of patients with COVID-19 who already had heart disease found hepatomegaly and persistent inflammation.[50] In another study, it was stated that in addition to the above-mentioned factors, cytokine storms caused by an excessive immune response to the virus could be another factor that leads to liver damage.[51,52] An excessive increase in proinflammatory cytokines has been observed in a high percentage of patients with COVID-19 with a decrease in T cells and an increase in neutrophil counts. Therefore, it has been concluded that lymphocytopenia and CRP levels are independently associated with liver damage, which shows the role of cytokine storm in liver dysfunction.[51,53] Liver damage can also be a result of hypoxia, leading to severe respiratory failure.[51] The death rate in patients with cirrhosis increased based on the Child-Pugh class (A [19%], B [35%], C [51%]), and the leading cause of death was the respiratory failure (71%). Acute hepatic decompensation occurred in 46% of patients with cirrhosis, of whom 21% had no respiratory symptoms.[54] According to various studies, the ACE2 receptor is also expressed in the spleen and hilar lymph node. Studies have shown that in patients with severe pulmonary involvement, there is a sharp increase in spleen size, and this increase in the CT scan of the patient is related to the disease severity.[55] In the spleen, the nucleocapsid protein of the virus is distributed in the red pulp and blood vessels. There is also evidence that COVID-19 directly affects the spleen and lymph nodes and causes severe tissue damage such as lymph follicle depletion, splenic nodule atrophy, histiocyte hyperplasia, and lymphocyte depletion.[56,57] Another study also found that COVID-19 induced microvascular thrombosis and splenic necrosis.[58] Many studies have reported that lymphocyte depletion is expected in elderly patients with severe COVID-19. A study using immunofluorescence staining discovered that the number of CD11b-positive immune cells, including macrophages, in the spleen of patients with COVID-19 who died was remarkably more compared to control patients and that SARS-CoV-2 S protein was detected in more than 67% of the samples. Besides, the incidence of apoptosis measured by two apoptotic markers, TUNEL and caspase-3, was higher in spleen cells of COVID-19 patients compared to the control patients (15.8% of TUNEL-positive cells in the control group and 60.1% in patients with COVID-19). According to a report, SARS-CoV-2 may lead to higher rates of apoptosis and lower rates of immune cell autophagy in COVID-19 patients. The study also found that in the spleens of COVID-19 patients, the white pulp was reduced, while the red pulp was congested. They also reported that SARS-CoV-2 S protein was expressed in 68% of splenic tissue cells.[59]

Ocular Manifestations

In addition to the diseases mentioned above, ocular manifestations have been widely observed in COVID-19 patients. Based on research, the eyes should be considered organs in which SARS-CoV2 can inoculate.[60,61] Hence, ocular manifestations can help physicians in treating and detecting COVID-19 patients. ACE-2 receptors are also present in the corneal limbus, and the SARS-CoV-2 virus binds to the host cells with the help of transmembrane protease serine 2 (TMPRSS2). Based on different studies, ocular manifestations can be the initial presentation of the disease or occur during hospitalization.[62] According to various studies, ocular manifestations have been seen in COVID-19 patients. Scientists reported that SARS-CoV-2 has been detected in different body fluids such as blood, feces, and pulmonary secretion.[51] Various studies have been conducted globally to confirm the presence of SARS-CoV-2 in ocular secretion. For this purpose, conjunctival swabs were used to obtain tear and conjunctival secretions of the patients for RT-PCR tests. Different rates of positive results were reported in previous studies.[51,63] Based on a study, 5 patients out of 32 patients with no ocular manifestations had virus RNA in eye secretions.[64] According to another study on 49 patients with confirmed COVID-19, four patients had positive RT-PCR results. As described earlier, the most critical manifestations of COVID-19 were related to pulmonary complications[65]; however, based on studies, eyes are also important in the transmission and inoculation of the virus. Based on recent studies, the main ocular manifestations of COVID-19 are conjunctival congestion, conjunctivitis, epiphora, and chemosis. Besides, it has been observed that having ocular manifestations is related to more severe infection.[65] The American Academy of Ophthalmology mentioned conjunctivitis as a presenting symptom of COVID-19.[66].In a study conducted on 535 COVID-19 patients, 27 cases had conjunctival congestion, 3 of whom had it as an initial symptom. Furthermore, based on six different studies conducted in China, different rates of conjunctivitis (0.81%, 3.33%, 4.68%, 31.57%, 1.1%, and 3.57%) were reported in COVID-19 patients. This wide range may result from differences in age, gender, and severity of the disease.[67] More ocular manifestations such as keratoconjunctivitis, episcleritis,[68] and dacryoadenitis[69] are also crucial. Additionally, hyperemia was observed in this pandemic.[70] To treat and manage ocular diseases resulting from COVID-19, physicians have prescribed

medicines and used strategies. Several drugs and procedures were prescribed and used, including ribavirin, azithromycin fluid, dexamethasone, eyelid hygiene, artificial tears, and eye washing with saline.[71,72] Moreover, based on other studies, valacyclovir, moxifloxacin, and fluorometholone were also used in patients.[68,73] Two other essential drugs in COVID-19 infection are hydroxychloroquine (HCQ) and chloroquine (CQ), which have side effects that should be concerned in long-term use. Additionally, in high dosage, they may cause irreversible maculopathy in short-term use.[74,75] To decrease systemic inflammation and prevent pulmonary fibrosis, many hospitalized COVID-19 patients are given corticosteroids. In addition, dexamethasone is prescribed, which can potentially reduce the mortality rate in patients receiving oxygen support. Although corticosteroids have efficacy in treating COVID-19 patients, they may cause cataracts and glaucoma in long-term use. It has been discovered that dexamethasone induces nuclear and posterior subcapsular cataracts. The administration of systemic steroids for COVID-19 may increase glaucoma cases, leading to higher demand for surgery and medications.[76] Orbital apex syndrome has been described in a COVID-19 patient.[77] It involves the optic nerve, oculomotor nerve, trochlear nerve, and the first division of the trigeminal nerve, which may lead to ophthalmoplegia, vision loss, and pain in the eye.[78] Managing and treating COVID-19 patients with ocular manifestations is crucial; therefore, physicians, especially ophthalmologists and health care workers, need to use suitable personal protective equipment such as face shields to protect themselves.[79]

Hematological Manifestations

COVID-19 is a systemic disease, and besides the respiratory system, it has impacts on other organs. Blood and its components are crucial in the detection of inflammation and infection. Various studies have evaluated white blood cell (WBC), red blood cell (RBC), platelets, coagulation factors, and biomarkers that increase or decrease in a patient with COVID-19. These parameters are related to the disease severity, hospitalization, and other important factors.[80] ACE-2 receptors by which SARS-CoV-2 binds and invades the host cells are also expressed on lymphocytes, which is a cause of viremia. Studies have been conducted to assess blood indices, and each one of them gives essential information.[81] A high throughput study on COVID-19 patients' peripheral blood showed changes in miRNAs. Thirty-five up-regulated miRNAs and 38 down-regulated miRNAs have been identified in patients with COVID-19, among which miR-16-2-3p had the highest level, while miR-627-5p had the lowest level. Additionally, miR-618 and miR-6501-5p levels have been 1.5 times higher in COVID-19 patients compared with healthy individuals.[82,83] Evaluation of the level of miR-200c-3p in mildly affected, severely affected, and COVID-19 patients with respiratory disorders indicated that the highest level of miR-200c-3p was observed in the group with respiratory disorders.[84] Based on a study by Gustafson et al, there is a correlation between some miRNAs in peripheral blood and mortality of severe COVID-19. Their study indicated that miR-181a-5p, miR-199a-3p, and miR-339 are associated with COVID-19 mortality and can be used for determining the severity and mortality rate of COVID-19.[85] miRNA level also changes in deceased cases. According to a study by Giuliani et al, some miRNAs, such as miR-320b and miR483-5p, have been up-regulated in deceased patients in comparison with those who survived.[86]

White Blood Cell and COVID-19

Lymphopenia is a hematological finding which presents in viral infections. Lymphopenia has been observed initially and is considered a marker. Lymphopenia is an abnormality that has been seen in lots of COVID-19 patients during the pandemic. Lymphocytes express ACE-2 receptors. The virus may directly attack lymphocytes, which can cause apoptosis. Additionally, increased lactic acid levels in COVID-19 may lead to reduced lymphocyte proliferation. The cytokine storm is another factor that causes impairment in lymphocytes.[87]

Different studies and surveys have been conducted in this field. According to a study by Guan et al on 1099 patients, 83.20% had lymphopenia as an initial finding, and it was more prominent in severe cases (96.1%).[81] In another study by Wu et al, the prevalence of lymphopenia was 64%.[88] Increased leukocytes in COVID-19 patients must be discussed because they may indicate bacterial infection.

Neutrophilia

Another critical index that is under observation is neutrophilia. Many COVID-19 patients have neutrophilia because of the cytokine storm. According to a study by Wu et al on 201 patients, 68 patients had neutrophilia. Additionally, 84 patients had developed ARDS, and 44 out of them passed away, indicating a relationship between ARDS development and neutrophilia.[88] Fan et al studied 67 COVID-19 patients and discovered that neutrophilia was common in patients who required intensive care.[49]

Leukocytosis and Leukopenia

WBC count is related to severe and mild COVID-19; hence, scientists need to conduct more surveys to evaluate them. According to a study by Guan et al on 1099 patients, 33.7% had leukopenia at admission.[80] However, some cases had different results. Based on the results of a study by Hu et al on 323 patients, patients with severe disease also had leukocytosis.[89] A meta-analysis of 38 studies found that 69.7% of patients had normal leukocyte count,

25.9% had leukopenia, and 12.6% had leukocytosis.[90]

Platelets

Abnormal platelet count is expected in viral diseases and is not specific to COVID-19.[91] Several studies have been conducted to determine the role of platelets in the detection and prognosis of this disease. According to surveys, the platelet is a crucial parameter in disease severity, hospitalization, and mortality rate.[49,92] Based on a meta-analysis by Lippi et al on nine different studies, 1799 COVID-19 patients were involved, and 399 (22.4%) had severe COVID-19. These results showed that platelet count is remarkably lower in patients with a more severe disease.[93] Different factors may cause a decrease in platelet count in COVID-19 patients, such as underlying diseases, drug-related thrombocytopenia, cytokine storm, and immunological causes. Thrombocytopenia in COVID-19 can be caused by endothelial damage, which activates platelets and causes consumptive thrombocytopenia. There is also a direct effect on bone marrow that affects platelet production and immune function.[49,87]As reported in a study on 1476 patients, thrombocytopenia was seen in 72.7% of patients who passed away, while this rate was 10.7% in survivors.[94]

Red Blood Cell

Hemoglobin is another index that is observed. According to previous studies, reduced hemoglobin is associated with a higher mortality rate in many diseases.[95]COVID-19 is not an exception, and studies showed that hemoglobin value in COVID-19 patients is lower and is related to a more severe disease.[96,97] Similar to platelets, red blood cell count decreased for reasons such as the direct attack of the virus, structural similarity between spike protein and hepcidin, and down-regulation of iron metabolism.[49] A recent survey by Jacobs and Booth indicates a relationship between COVID-19 and autoimmune hemolytic anemia) AIHA(.In their meta-analysis, 50 patients with confirmed COVID-19 had AIHA and had a 19% mortality rate.[98]

C-Reactive Protein

CRP is an inflammatory factor that elevates infections and inflammation. In many viral diseases, including severe acute respiratory syndrome, the Middle East respiratory syndrome, and H1N1 influenza, increased CRP levels have been seen and reported.[99] CRP is increased in COVID-19 patients as well. Based on a study by Chen et al, CRP was elevated in 86% of patients.[100] Furthermore, in a study by Liu et al, CRP was greatly augmented in COVID-19 patients.[101] Similar to other parameters, CRP is related to the mortality rate. A survey by Ruan et al on 50 patients showed that CRP level was lower in survivors.[102]

Interleukin 6 and Lactate Dehydrogenase

Interleukin 6 (IL-6) is a factor for B-cell differentiation; it is a multifunctional cytokine that helps the immune response, hemopoiesis, the acute phase response, and inflammation regulation. Different types of cells produce IL-6, which can affect many cell types. Moreover, it has a unique receptor system and, as a result, has multiple biological activities.[103] IL-6 is also related to disease severity and poor prognosis, according to studies.[104-106]As reported by Chen et al, IL-6 value as an inflammatory biomarker was elevated in about 52% of patients at admission.[100] The oxidation of pyruvate to lactate is catalyzed by an intracellular enzyme called lactate dehydrogenase (LDH), which is commonly tested in various diseases. Increased serum LDH level, especially in tumors and inflammations, is associated with poor prognosis.[107] Severe infections may cause tissue damage mediated by cytokines, which can cause LDH secretion. As LDH (LDH-3) exists in pneumocytes, it is expected that in more severe COVID-19, a higher amount of LDH will be secreted.[108] LDH acts as a marker of cell and tissue damage in the body, which is used for patient observation. LDH has been increased in different surveys. Chen et al[100] reported that LDH level was high in 76% of patients. Moreover, as stated by Wan et al[109], LDH level was higher in patients with a more acute condition. As reported by Fan et al, raised LDH levels were seen in patients admitted to an intensive care unit.[49]

Musculoskeletal Disorders

In addition to pulmonary symptoms of COVID-19, innumerable extrapulmonary manifestations, especially musculoskeletal manifestations, were frequently reported during the pandemic.[110,111] Despite the lack of deep investigation into the musculoskeletal disorder of COVID-19, a synovial and muscle biopsy and joint fluid analysis may be able to reveal how massive the spread of the virus to the entire body is. The presence of SARS-CoV-2 in the skeletal muscles, joints, or bones has not yet been approved and the symptoms are mainly attributed to inflammatory and/or immune responses.[112] Epidemiological data from the pandemic identified myalgia, muscle deficiency, osteoporosis, and osteonecrosis as prevalent outcomes in patients with mild to intense forms of the disease. Further remarkable musculoskeletal disorders in COVID-19 patients have not been investigated in long-term follow-up.[113] Furthermore, direct viral infections, cytokines, and pro-inflammatory signaling molecules affect changes in skeletal muscle tissue. As the number of patients and survivors of COVID-19 increased, numerous reports of neuromuscular and rheumatologic manifestations related to both the virus and the treatment/hospital course were conducted.[114] The reports of musculoskeletal symptoms are even more concerning since they suggest that inflammatory reactions exacerbate the anti-inflammatory effects of such drugs.

Some articles reported that a wide variety of physical features are related to the persistence of musculoskeletal signs.[110,115] A single-center cohort study conducted on 300 patients, two weeks and 1 month after hospitalization, revealed the fact that back, low-back, and neck pain, arthralgia, myalgia were correlated with higher body mass index (BMI).[116] Musculoskeletal and iatrogenic manifestations of COVID-19 could be diagnosed with ultrasound, CT, and MRI that show muscles, nerves, joints, soft tissues, and bone.[117]

Skeletal Muscle

Myalgias and generalized weakness were manifested in 25 % to 50 % of COVID-19 patients. Some studies proposed that muscle pains do not increase in COVID-19 patients, although myalgias is a significant factor in the intensity of the disease.[118] One study on 2014 patients with COVID-19 in Wuhan reported that neurological symptoms were observed in 36% of the patients, with an impact on motor control and muscle activity.[119] The mechanistic effects of COVID-19 on skeletal muscles have yet to be investigated entirely due to the nature of the infection. However, it was noted that signaling molecules such as Interferon gamma (IFN- γ), IL-1b, IL-6, IL-17, and Tumor necrosis factor alpha (TNF-α) are elevated in COVID-19 patients and may induce muscle fiber proteolysis and reduce protein synthesis.[113] Proliferation and differentiation of satellite cells which directly contribute to muscle fiber growth as progenitor cells can be blocked by IL-1b and TNF-α. Furthermore, IL-1b and IL-6 can induce muscle fibroblast activity and lead to fibrosis, which may increase susceptibility to injury.[120] The U.S. Centers for Disease Control and Prevention (CDC) recommends that corticosteroids should not be used for treating this infection which may result directly in muscle atrophy and weakness.[113]

Bone and Joint

Bone and joint disorders of COVID-19 are less known than skeletal muscle disorders. Arthralgia is prevalent among patients, especially in combination with myalgia which leads to reduced bone mineral density (BMD). It is suggested that corticosteroids, which are among the major therapies that attempt to decrease the inflammation that occurs in the primary infection and following early rehabilitation and recovery time, cause reduced BMD that occurs independently in both SARS and COVID-19 patients.[120] Hypercoagulability also leads to large-vessel stroke and osteonecrosis in several patients of both COVID-19 and SARS. Hypercoagulability, vessel inflammation, and leukocyte aggregation may affect microvascular blood flow and result in the development of osteonecrosis.[121] Systemic inflammation plays a key role in bone and joint tissue physiology in patients with COVID-19. CXCL10, IL-17, and TNF-a can induce osteoclastogenesis and decrease osteoblast proliferation and differentiation. In some patients, IL-1b, IL-6, and TNF-a can result in arthralgias or the development of osteoarthritis.[112]

Conclusion

The high risk of COVID-19 progression might be associated with extrapulmonary organ involvement. Extrapulmonary manifestation of SARS-CoV-2 infection can be the only presentation of infection during the initial stage of the disease. Therefore, identifying these atypical manifestations would improve the early diagnosis of patients, which helps reduce the transmission of COVID-19 in society and also select appropriate therapeutic interventions with personalized approaches to limit the risk of decompensation. Moreover, this issue might be correlated with failure to make an accurate diagnosis or delayed diagnosis by clinicians and radiologists. Further research is required to validate the extrapulmonary manifestations of SARS-CoV-2 infection.

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Competing Interests

The authors declare no conflict of interests.

Ethical Approval

Not applicable.

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