

<https://doi.org/10.56770/jcp20259110>**COMPLICATIONS ASSOCIATED WITH COVID-19: A COMPREHENSIVE REVIEW****Muhammad Naeem** 

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ABSTRACT

SARS-CoV-2 is extremely contagious, and most people in the general community are at risk of infection. The coronavirus disease (COVID -19) is caused by SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2). After entering the human system via the orofecal route, it attaches with ACE-2 (angiotensin converting enzyme, 2) receptors leading to pathophysiological complications. ACE-2 is found in various organs and tissues, which is consistent with the vast range of clinical systemic symptoms and multiorgan failure associated with COVID-19. Its radius of clinical demonstration typically includes fever, nonproductive cough, and fatigue, often with pulmonary involvement. While much of the attention has been on the pulmonary problems, emergency clinicians should be aware of the other related complications, contributing significantly to the disease's mortality. The involvement of ACE leads to morbid complications, including respiratory, hepatic, cardiac, renal, and gastrointestinal damage. This brief study will provide a targeted summary of COVID-19-related problems, including hematological, cardiovascular, neurological, gastrointestinal, and other rare complications

Keywords: Complications, COVID, SARS-CoV-2, Related problems.*Corresponding Author. E-mail: naeem.mahar@salu.edu.pk**INTRODUCTION**

In January 2020, during a pneumonia epidemic, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus was discovered in the city of Wuhan, the Hubei Province of China [1]. Ever since, this virus has swept over the world, infecting 516 million individuals, and as of May 3, 2022, it has killed 6.26 millions of people [2]. The Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV one and 2 are cause of severe pneumonia with observed fatality rates of thirty six percent approximately 3 percent and ten percent (36%, 2.9%, 9.6%) respectively [3]. There are additional four types of human coronaviruses are HKU1, OC43, 229E, and NL63, which might cause self-limiting mild infection with a few symptoms [4].

This paper covers the transmission of SARS-CoV-2, capacity to invade target tissue, clinical and laboratory observations, pathological findings, serological diagnosis, and safety issues, provides a comprehensive overview of the complications connected to the Coronavirus Disease 19 pandemic. SARS-CoV-2 resembles quite a bit with SARS-like coronaviruses found in bats [5]. Genome study and comparing with previously identified coronavirus

genotypes revealed that SARS-CoV-2 is unlike from conventional coronaviruses due to optimum specificity for the ACE2 receptors & a cleavage point at the spike Protein S1 and S2 intersection that controls infection rate and host species [6]. Structure studies on the SARS-CoV-2 RBD (Receptor binding Domain) or ACE2 complexes reveal that the SARS-CoV-2 RB Domain attaches with ACE2 receptor more strongly than SARS-CoV RB Domain. SARS-CoV-2 RB Domain provides a colossal binding interface and go in for additional interactions with ACE2 receptors. The internalization and endocytosis of SARS-CoV-2 by T-cells/thymocytes and lymphocytes are regulated by the S proteins [7].

Like other viruses effecting the respiratory system, SARS-CoV-2 transmits most effectively and infectiously via nasal passages. The most widely recognized way is droplet transmission, though aerosols might also be involved [8]. Just like SARS-CoV, the oral & fecal pathway may also be a route through which this virus spreads. SARS-CoV-2 RNA was also discovered in a patient's excreta who had COVID-19 pneumonia [9].

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Sewerage may thus contribute to the escalation of SARS-CoV-2. Given this, specialized therapy can both confine and inactivate the virus ought to be taken into account [10].

Depending on Weibull distribution, it was determined that the average incubation duration was 6.4 days, with a possible range of 2.1 to 11.1 days. Similar forecasts have been made by other scholars. In 95 percent of patients, the median incubation bout was 5.1 days, and over 97 percent of infected beings displayed prodrome within 11.5 days of exposure, according to Lauer et al. The 14-day effectual monitoring period endorsed by health establishments is therefore supported by the evidence [11].

The clinical manifestations of SARS-CoV-2 infection can range from moderate to severe, and a significant proportion of the population is not symptomatic. The three most frequently reported symptoms are fever, cough, and a shortness of breath. Many mottling and ground-glass opacity are frequently seen on lung X-rays in pneumonia patients [12]. 2–10% of COVID-19 patients have complained about diarrhea, vomiting, and stomach pain, while almost 10% of patients have complained about nausea and diarrhea prior to the start of a fever and other respiratory complaints [13].

Patients with COVID-19 frequently had higher WBC, neutrophil, CRP, LDH, AST, and ALT blood levels, reduced lymphocyte and eosinophil, and substantially lower hemoglobin values. Furthermore, the severity of COVID-19 infection can be accurately predicted by early CRP serum levels [14].

Although the lungs are the primary organ affected by coronavirus, it also is important to monitor the gastrointestinal, renal, cardiovascular, central nervous system, liver, and eyes because of the broad presence of ACE2 receptors in these organs [15].

Common side effects include cardiotoxicity, inflammation of cardiac muscles, myocardial infarction, cardiac arrest, cardiac arrhythmias, and thrombotic events. Closely monitoring high-sensitivity cardiac troponin might be useful [16].

As a result of the so-called "cytokine storm" in acute respiratory distress syndrome a patient's condition may suddenly worsen and die from numerous organ failures." Monocyte (white blood cells) chemoattractant protein 1, kupffer cell inflammation protein 1-a, tumor necrosis factor-a, interleukin (IL)-2, IL-7, granulocyte colony-stimulating factor, interferon-c inferential protein-10, and elevated levels of these proteins have all been reported in severe COVID-19 cases. These proteins are also known as increased IL-7, granulocyte colony-stimulating factor, interleukin (IL)-2, Additionally, higher levels of ferritin and IL-6 indicate a higher likelihood of dying from

virus-induced hyper inflammation [17]. Based on research, patients with COVID-19 pneumonia and high level of blood interleukin 6 are administered tocilizumab (IL-6 receptor blocker) to eliminate inflammation of the airways.

Levels of D-dimer have been connected to the intensity of COVID-19. Individuals infected by COVID19 virus have remarkably increased D values in comparison to those without infection. Increased D-dimer values may suggest a likelihood of generalized coagulopathy in those with severe COVID-19, necessitating the use of anticoagulant therapy [18]. Heparin may also impede proteases intricate in virus contagiousness. SARS-CoV-2 ingress requires the crevice of the S₁ and S₂ protein and subsequent melding of S₂ to the cell membrane. Heparin prevents host proteases like factor Xa, cathepsins, TMPRSS (cell surface transmembrane protease/serine proteases), trypsin, and furin, which are necessary for the latter, from working [19].

SARS-CoV-2 has been linked to symptoms ranging from a simple headache to more severe encephalopathy and dysexecutive disorders in the central nervous system. For this review, neurological complications will be divided into central nervous system (CNS) effects, peripheral nervous system (PNS) effects, and skeletal and muscular injury caused by SARS-CoV-2. Despite such high rates of illness and mortality, little research has looked into the neurological repercussions of SARS-CoV-2 infection [20].

During the COVID-19 epidemic, gastrointestinal problems in severely ill individuals provide a diagnostic and management conundrum. The host receptor angiotensin-converting enzyme-2 (ACE-2) has also been extensively expressed in respiratory cells and gastrointestinal regions such as the glandular cells of the gastric, duodenal, and rectal epithelium. This shows that SARS-CoV-2 can attack the digestive system and spread through that pathway. In addition to respiratory symptoms, gastrointestinal symptoms such as diarrhea, nausea, vomiting, and abdominal pain may occur. SARS-CoV-2 RNA has been found in stool specimens and rectal swabs of COVID-19 patients [21].

A few uncommon clinical symptoms can be a great concern for clinicians. Pneumomediastinum is one example. While ground-glass opacity (GGO) is the most prevalent radiographic lung characteristic corresponding to COVID-19 pneumonia, other unusual pulmonary features include localized lobar or segmental accumulation without GGO and distinct mediastinum [22]. There has also been a rise in the incidence of acute limb ischemia in COVID-19 patients. COVID-19 individuals who arrive with acute lower extremities ischemia and venous thromboembolism due to arteriosclerosis obliterans have a poor prognosis and higher mortality [23]. Other Uncommon consequences of

coronavirus disease (COVID-19) pneumonia include spontaneous pneumothorax (SPT) and pneumomediastinum (SPM). The actual number of cases and factors associated remains unclear [24].

PATHOPHYSIOLOGY

Life Cycle

The COVID-19 life cycle follows a set of five steps. The first step is the attachment of Corona virus to the host receptor on the surface, followed by entrance into the host cell, where it releases its contents. This process is called penetration and is mainly done by membrane fusion or endocytosis. The third step is biosynthesis, in which viral proteins are synthesized. Spikes, membrane, envelop, and nucleocapsid is basic proteins that make up the structure of coronavirus. The viral RNA penetrates the host cell's nucleus and uses its mRNA for replication. After this, the new virus particles are formed in the next step called maturation. And then, the final step is called release [25].

Structure

Spikes are the projections on the surface of the virus responsible for attachment of virus to host cell and determine the diverse nature of coronavirus. It is a transmembrane glycoprotein that is trimetric. S1 and S2 are two subunits of spikes, among which S1 is liable to bind with the receptors of the host cell, and S2 initiates the fusion process between the viral and host cell membrane.

Binding at the receptor site

Angiotensin-converting enzymes type 2 are the receptors responsible for binding SARS-CoV 2 spikes on the host cell [26]. These ACE2 receptors are highly expressed in lung epithelial cells, kidneys, bladder, ilium, and heart [27]. Further investigation is required to discover the other potential binding receptors on the host cell surface.

Activation

The coronavirus spike can be activated and cleaved by various proteases as it is peculiar compared to other viruses [28]. After binding, cleavage of spikes takes place by protease enzyme [29]. This cleavage occurs at the cleavage site of S1 and S2, but both of these subunits remain bound with a bond other than covalent. S1 subunit help to stabilize the S2 subunit anchoring into the membrane [30]. Irreversible and conformational changes cause the activation of spikes for membrane fusion. These changes occur by dissociation at the S2 site. SARS-CoV- 2 undergoes furin cleavage at the S1/S2 site, making it more pathogenic than other coronaviruses [31].

Immune response

Lung injury in the distal airway is usually observed even at the outset of infection. This occurs when virus binds with ACE2 receptors and destroys the epithelial cells of the lungs as these receptors are present on these epithelial cells [32]. Impaired immune response and inflammatory response

(uncontrolled) are the results of infection caused by COVID 19 [33]. The host's immune response is triggered by pro-inflammatory cytokines produced after pathogen recognition.

Along with activating the immune response, the coronavirus is also responsible for uncontrolled inflammatory reactions, i.e., the release of pro-inflammatory cytokines can result in lymphopenia, monocyte, granulocyte, and lymphocyte abnormalities. Endothelial cells are one of three major components of innate immunity, while the other two are dendritic cells and alveolar macrophages. Endothelial injury may result in microvascular permeability. Thus, it can assist in the invasion of the virus.

Macrophages are present on the apical epithelial side, while Dendritic cells can be found under the epithelium. these cells are fighters of innate immunity against viruses till the activation of adaptive immunity [34]. Dendritic cells and macrophages can phagocytize the epithelial cell after being infected by the virus, thus leading to activation of T cell response [35].

After this, the adaptive immune response is activated, which is characterized by the production of T cells (for the killing of infected cells), B cells (to produce antibodies), and cytokines (to produce an inflammatory response). This immune response activation is crucial for removing the virus from the host body. However, they are also involved in severe tissue damage [36]. As a result, CD4 and CD8 T cells are formed. The first one is involved in producing antibodies through B cell activation, while the second one is involved in killing infected cells. These are pathological cytotoxic T-cells that kill pathogens and cause lung injury [37, 38]. Additionally, increased interleukins two and tumor necrosis factor-alpha have also been observed in critical patients [39].

Immunological studies have shown a marked decrease in T-cells (lymphopenia), natural-killer (NK) cells, and B (beta) cells. The overall percentage of monocyte, basophils, eosinophils, and natural killer cells has also been decreased in severely affected patients [40]. Reports indicate an increased assemblage of pro-inflammatory cytokines (IL 1 β , IL6, IL10), monocyte chemoattractant proteins, granulocyte-colony stimulating factor, macrophages inflammatory proteins in plasma and tumor necrosis factor-alpha.

Levels of IL8, which is a chemoattractant for T cells and neutrophils, along with IL6, have also been observed, produced by infected lung epithelial cells [41].

Innate and adaptive immunity can be activated by SARS-CoV 2. Impairment in any of these two immune responses may result in tissue damage that may be harmful. Specific antibodies for SARS-CoV-2 can be detected in an infected patient.

Clinical improvement has been discerned in some adversely ill victim of COVID-19 when treated with neutralizing antibodies. Figure 2 shows the steps involved in coronavirus infection, the resultant immune response and possible therapy to halt these reactions.

Hematological Complications

The involvement of hematopoietic system components is frequent in serious conditions and is linked to poor prognosis and mortality. COVID-19 linked hematological symptoms include leukopenia, neutropenia, lymphopenia, dispersed intravascular coagulation, and thrombotic complications, all of which have therapeutic and clinical complications. A finer understanding of the pathogenesis of COVID-19 instigated hematological anomalies may be a guide to better treatment and a limiting the related morbidity and death rate.

Leukocyte count has been normal during the starting phase of infection. However, several reports have been witnessed of leukocytosis and leukopenia [42]. A study was conducted in China, and the percentage of leukopenia was found to be 33.7%, lymphopenia 82.1%, and for that leukocytosis, it was found to be 5.9% [43]. According to another study, the ratio of leukopenia in 511 patients was 43.1 %.

The presence of ACE2 receptors on lymphocytes can indicate that they can be a direct target of the COVID-19 virus which can ultimately cause lysis of lymphocytes [44]. The decline in the level of CD4 and CD8 may be due to the action of COVID-19 on lymphocytes (specifically T lymphocytes) [45]. Some proposed mechanisms behind this decline may include lymphocyte lysis via direct action ACE-2 receptor and autophagy of lymphocytes via pro-inflammatory moderators. Lymphocyte yield may also be reduced due to the decay of lymphoid tissue. However, it is not yet proved that COVID-19 can cause damage to the spleen and thymus. Another proposed mechanism can be the presence of oxidative stress, i.e., lactic acidosis [46, 47].

By comparing a pool of patients admitted to ICU with those not admitted in ICU, the development of neutrophilia was more observant in ICU admitted patients than those who were not admitted to ICU. In the first group, the neutrophil count was $11.6 \times 10^9/L$, and in the latter, it was $3.5 \times 10^9/L$ [48]. Lymphopenia has been observed as a clear measure of the presence of Covid 19 infection [49]. Increased white blood cells and decreased lymphocyte levels have been observed in diseased patients than in those who recovered from the infection. Similarly, in severe patients, the ratio of neutrophil to that lymphocyte is higher, and the ratio of lymphocyte to C-reactive protein is lower [50]. Platelet count from $100/mm^3$ to $150/mm^3$ has

been observed, indicating mild thrombocytopenia.

The occurrence of thrombocytopenia in SARS patients was reported to be up to 55%. Proposed mechanisms behind this fluctuation can be platelet activation due to injury at the endothelium, bone marrow infection, autoimmune activation against blood cells, or thrombus formation in the lungs. An increase in platelet counts at the initial level and then a decrease at a later stage has been observed. This fluctuation can worsen the patient's condition and increase the stay duration in the hospital [51].

Cytokine Storm Syndrome

It is a condition in which an unusual rise in cytokine production elicits an immunopathological response. This rise in cytokines may be due to some infection, or some drugs may also induce their production [52]. A spike in clinical findings has been observed seven to fourteen days after the start of early symptoms. A significant rise in pro-inflammatory molecules characterizes cytokines storm [53]. In severe incidence of COVID-19 elevated interleukins (2 & 7), monocyte chemoattractant protein 1, macrophage inflammatory protein 1- α , granulocyte colony-stimulating factor, interferon-gamma inducible protein, and tumor necrosis factor-alpha are characterization factors of cytokine storm syndrome [54].

In the case of COVID-19, infection attachment of the virus to endothelium leads to activation of the adaptive and immune response. As a result, cytokines are released that cause inflammation and ultimately elevate the permeability of vessels. Dyspnea and respiratory failure occur due to leakage of secretions into the alveoli [55, 56]. Fever is one of its signs, and it can be lethal in severe cases.

Cardiovascular, renal, and pulmonary complications are also associated with this syndrome. They are discussed in other sections of the article.

Thrombosis

Another emerging issue in COVID-infected patients is thromboembolism. In the initial reports of COVID-19 incidence of thrombotic events was not frequent, but later complications regarding venous and arterial thrombosis were reported [57].

Venous Thrombosis

Many infected patients have been diagnosed with thrombosis of the vein in the lower body. The coexistence of pulmonary embolism is also present in reports [58]. According to a study report on venous thromboembolism VTE occurrence, the percentage was 27% even when the patients were administered a standard anticoagulant dose for prophylaxis [59]. In another similar study where patients were administered a prophylactic dose of anticoagulant, the percentage increased from 11% to 34% (from day 1 to day 14) [60].

Arterial Thrombi

Arterial thrombotic complications have also been observed in COVID-19 patients, but several reported cases are less than venous thrombi. These occlusions may result in complications i.e. myocardial infarction, stroke, and in a few patients, it can lead to acute ischemia of limbs. According to a case study, 44 percent of patients were diagnosed with myocardial infarction. All of the patients were COVID positive and had an increased level of D-dimer. While in another study of COVID-19 positive patients, the percentage was 64%. However, level of D-dimer was normal in these infected patients [61, 62].

Causes of Thrombus Formation

Many factors could be responsible for thrombus formation during COVID infection. One of these possibilities is considered to be the excessive release of cytokines [63]. Cytokines can cause atrophy of endothelium. Hypercoagulability, acute respiratory distress syndrome (ARDS), and disseminated intravascular coagulation (DIC) can occur due to this atrophy.

The D-dimer level is increased in inflammation, an indicator of fibrin breakdown. This increased level can be an indicator of microvascular thrombosis. Micro thrombi in the lungs can be formed due to injury to the lungs. This results in an increased level of D-dimer [64]. D-dimer is also considered a good marker of venous thromboembolism in COVID-positive patients [65].

Anemia has not been observed commonly in COVID-19 infection. Complications associated with the coagulation pathway are also observed most of the time during COVID-19 infection [66].

A patient with high Troponin-T levels is likely to have a higher D-dimer, activated partial thromboplastin, and prothrombin time. Levels of D-dimer, fibrinogen, and fibrinogen degradation products have been increased. Similarly, prolongation in thromboplastin time and prothrombin time have also been noted [67]. D-dimer elevation can be a causative agent in developing ARDS (acute respiratory distress syndrome). The patient requires admission to ICU and mechanical ventilation, which can also lead to death.

Microvascular thrombi formation has been observed in COVID-infected patients. A pathophysiological explanation suggests that activation of immune response cause increased production of cytokines and procoagulating factors, i.e., von Willebrand factor and tissue factor. Free thrombin circulation results in fibrin clot formation plus fibrinolysis. The patient's admission must be given if his D-dimer level is increased by almost three or four times, even if symptoms are not visible.

Myocardial injury in COVID-19 can result in increased deaths during infection [68].

The rise in C-reactive protein and procalcitonin levels is observed in COVID-infected patients. Procalcitonin can be indicative of secondary infection by bacteria. This situation can worsen the symptoms of infection. [43] Myocardial injury, elevated Troponin-T levels, acute respiratory distress syndrome, and death in COVID-19 infection have been associated with increased C-reactive protein.

Rare Hematological Complications

Patients with Sickle cell disease experience more serious complications if infected by the COVID-19 virus. They are immunocompromised and are comparatively more prone to experience severe pain and acute chest syndrome during COVID infection, as in the case of influenza (H1N1) [69]. Immune thrombocytopenia is a rare occurrence along with COVID-19 infection. Only one case of a female (65 years) known to have a history of autoimmune hypothyroidism has been reported [70].

Cardiovascular Complications

Cardiovascular problems related to covid -19 include venous thromboembolic events, myocarditis, heart failure, myocardial injury, and acute myocardial infarction. These complications can contribute significantly to the death rate linked with Covid-19 [71].

In covid-19 patient immune system functions are altered, and the overall metabolic demand is increased [72]. Destabilization of vascular plaque may occur due to inflammation in the system [73]. The angiotensin-converting-enzyme 2 receptors present in cardiac tissues may also be damaged by the virus [74]. These events collectively can lead to cardiovascular issues in patients [75]. Underlying cardiovascular diseases may increase the severity of covid-19 infection [76]. According to a study conducted on 44,672 covid-19 patients, the incident of death rate is increased five times if the patient has a CVD history.[78] Among all the complications of covid-19 cardiogenic shock is the most critical condition [77].

Myocardial Injury

The first study on myocardial injury due to covid-19 was conducted in Wuhan, China, on 41 patients. Among them, troponin I (high sensitivity) level was higher than the normal limit of 28 pg/ml in five patients [78, 79]. Elevated troponin level is considered to be linked with severity of outcomes, including mortality [80, 81]. In later studies, the myocardial injury was observed in 7-17 percent of hospitalized individuals with high troponin levels. While in the case of admission to the ICU (intensive care unit), this percentage range was between 22-31.

Myocardial injury and myocarditis have also been observed in middle east respiratory syndrome coronavirus (MERS-CoV). High troponin levels were observed in that condition due to increased

physiological stress on the heart and hypoxia [82]. According to another study, 7% of deaths due to covid are related to myocarditis [83].

It is challenging to diagnose myocarditis in covid-19 patients. Common presentations include dysrhythmia, chest pain, acute dysfunction of the left ventricle, and dyspnea. Electrocardiograms can be used as markers to detect the severity of the disease. Electrocardiogram abnormalities such as ST wave segment oddities can be used in diagnostic findings. These changes may be due to myocardial inflammation. It is encouraged to perform an echocardiogram. It gives the evaluation of focal wall motion dysfunction. Defects in wall motion are not observed in myocarditis during covid infection [84].

Acute Myocardial Infarction

During covid infection, inflammation and coagulability are high. Due to this reason, the risk of acute myocardial infection is present there. Due to high inflammation in the system, there are chances of plaque erosion in atherosclerosis [85].

In acute myocardial infarction during covid-19 infection, the treatment of choice is percutaneous coronary intervention. Personal protective equipment plus complete documentation of laboratory characterization is mandatory for PCI. According to the American College of Cardiology, fibrinolysis is opted for patients who have low-risk ST-elevation myocardial infarction without ventricle involvement and for those patients who have lateral acute myocardial infarction with no hemodynamic compromise.

Acute Heart Failure

It can be a predominant symptom of COVID-19 infection. Heart failure is associated with increased chances of mortality in patients infected with the coronavirus. According to a study, the estimated occurrence of heart failure in COVID-19 is 23 %. The improper heart functions must be considered prior to administer intravenous fluids. Rapid fluid replacement must be avoided.

Dysrhythmia

A pounding heart is found to be one of the primary presentations of COVID-19 [86]. Excessive inflammation, hypoxia, and abnormalities in metabolism may lead to abnormalities in heart rhythm. Other causes of these abnormalities may be fever, anxiety, and hypoperfusion. Different dysrhythmias are observed in COVID-19 patients, among which sinus tachycardia is most frequent. Acute myocarditis, acute coronary syndrome, and myocardial injury must be taken into consideration if a relation is found between increased troponin levels in serum and the abnormal rhythms.

Venous Thromboembolic Events

A high risk of thrombosis is present in these patients. Coagulation pathway abnormalities are evident in COVID infection. These abnormalities, dysfunction of other vital organs, and evident

inflammation collectively contribute to venous thromboembolic events. Anticoagulant therapy can decrease the chances of mortality in these patients.

Neurological Complications

The SARS CoV-2 outbreak came with neurological symptoms in a large number of infected populations. Among the most common symptoms observed in the central nervous system were headache, ataxia, seizure, impaired consciousness, and dizziness. Those with the peripheral nervous system had a smell, vision, and taste impairment. Due to immune system activation, certain diseases, i.e., Guillain barre Syndrome, can be present even after recovery from infection. reference the same

Among other common features observed in Covid-19 patients is neurotropism [87]. The virus can involve the nervous system directly or indirectly. In a direct mechanism, the virus invades nervous tissues during the acute phase, and in the second case, the invasion is mediated by the immune system. The immune-mediated response may take days, even months [88]. Other possible mechanisms that can lead to neurological complications are immune injury, hypoxia, and attack of the virus on the angiotensin-converting enzyme [89].

Toxic encephalopathy & encephalitis are some of the neurological manifestations caused by the COVID virus. In the first report on neurological complications, the percentage of patients was, 36.4 percent that suffered from the peripheral and central nervous system and skeletal muscle disturbances. Occurrence of Hypoxic encephalopathy 20% and thrombotic complications 31% have been observed in severely ill patients [90-92].

Other observations include acute demyelinating polyneuropathy and Miller Fisher syndrome [93, 94].

Demyelination of nerve fibers, Neuronal Ischemic alterations, the presence of lymphocytes and monocytes in the walls of vessels, and particles of SARS-CoV have been detected in brain autopsy [95].

Inflammation and hypoxia collectively lead to hypercoagulability. Dysfunction of Vascular endothelium and coagulopathy can be contributing factors in intracerebral or subarachnoid hemorrhage and bleeding diathesis while inflammation of the membrane can contribute to meningitis and encephalitis. The presence of SRAS-CoV-2 has been observed in CSF (cerebrospinal fluid) via polymerase chain reaction (RTPCT) [96].

Neurological manifestations have been reported to be 34% by a study in Wuhan, among which complications associated with a skeletal muscle injury, central nervous system(CNS), and peripheral nervous system (PNS) were observed [97]. According to another study, the rate of headache and confusion in patients with COVID

infection was 8% and 9% [98]. Symptoms commonly associated with CNS are dizziness and headache, and those with PNS are hyposomnia and dysgeusia. Agitation, ankle clonus, and tendon reflexes have also been observed in COVID infected patients experiencing ARDS.

It is observed that neurological complications associated with COVID infection are very common, increasing as the disease progresses. Neurological syndrome associated with COVID infection is categorized into Guillain-Barre Syndrome, Stroke, and meningoencephalitis. Additionally, cognitive impairment is also observed in some patients. Reference of this article [99].

Gastrointestinal Complications

Involvement of the gastrointestinal tract is verified by the presence of the COVID virus in anal swabs and fecal test samples [100]. Gastrointestinal symptoms associated with COVID infection include diarrhea, nausea, vomiting, abdominal pain, anorexia, and GI bleeding [101]. Diarrhea and malabsorption occur due to enterocyte malfunction after GI mucosa gets involved [102].

Several proposed reasons can be contributing to GI complications in COVID infection. These can be the intestinal microbes [103]. Angiotensin-converting enzyme two receptors, 23 or use of certain medications [104]. ACE-2 receptors are found in glandular cells of epithelium in the duodenum, rectum, and stomach. They are few in number at squamous epithelium cells such as in mucosa of the esophagus and colon [105,106].

Some severe GI problems have been observed in COVID-infected patients. [103] Names of such complications include acute acalculous cholecystitis, extensive hepatic necrosis, and bowel ischemia. Gastrointestinal ischemia can lead to hypoperfusion of the bowel [107]. Ischemia and thromboembolic events can occur due to coagulopathy, which is a consequence of COVID infection.

Scarce data is available regarding ischemic GI complications [108]. Among ischemic gastric complications, mesenteric complications need attention as they may increase the risk of mortality [109]. Inflammation, hypercoagulability, endothelial dysfunction, vasculopathy, etc., are thought to be a potential pathological mechanism for ischemia. The exact pathogenic process involved is not clear. Ambiguities are also there regarding thromboembolic events, whether they are the result of this infection or not.

In the case of bowel wall ischemia, factors including positive pressure ventilation and viral enteritis must be considered [110]. Imaging results show dilated fluid-filled bowel segments with post-contrast intensification and lipid stranding or mesenteric inflammation in the surrounding area [111]. Other important findings by imaging are

portal venous gas and pneumatosis intestinalis. In severe cases, necrosis of the bowel wall is also observed, in which surgical resection is required [112]. CT scan reporting of the abdomen and pelvis must be considered in COVID infected patients having complaints of GI problems [113].

RARE COMPLICATIONS

Acute Limb Ischemia

An increase in the incidence of Acute limb ischemia has been observed recently in COVID-infected patients. It is a vascular complication. Ischemia in the lower limb may be due to thrombosis and atherosclerosis. It can be contributing factor to the high mortality rate during COVID infection.

Anticoagulant therapy can be an effective treatment. Tocilizumab has shown some beneficial results as well. It is an interleukin-6 inhibitor. Coagulation abnormalities in COVID-19 can lead to arterial and venous thrombosis. The most frequent cause associated with acute limb ischemia is arterial embolism. The chances of amputation are high in this complication. It can be avoided with early diagnosis and thrombolytic interventions.

Pneumomediastinum and Pneumothorax

Among other complications associated with COVID infection, pneumomediastinum and spontaneous pneumothorax have also been observed in a few patients. It can cause a rise in intrathoracic pressure leading to severe cough and ultimately damage to the alveoli wall. The formation of small cysts in the lungs may also be developed during the fibrotic stage of infection. The incidence rate and factors that can cause these complications are not clear yet.

According to a study, male gender, older age, and pre-existence of lung disease are found to be contributing factors. These two complications can be predictive of COVID-associated clinical conditions. The presence of free air in the mediastinum is characteristic of Pneumomediastinum. If it is spontaneous, it is benign and secondary; it may be due to some kind of infection, trauma, or rupture of the esophagus. The unusual finding of pneumopericardium in COVID-19 infection is still to be reviewed.

It is identified by air in pericardial space, which can occur as a result of traumatic chest wall damage or as a rare outcome of +ve pressure ventilation. Pericardium is a cushion that connects the vascular lining of big blood vessels to the anterior part of lungs, and it covers the heart. At higher intrathoracic tension, air from damaged alveoli main divide through the mediastinal parts of the lungs and also from the helium opening and reach the pericardium via venous sheaths having lower support of collagen. Most of the patients do not have symptoms, but some may present with instability in the hemodynamic system.

Renal Infarction

Abdominal visceral infarction is also reported in COVID patients. According to reports, the incidence of renal infarction is less, which is 0.1 - 1.4 %. The effect on the kidney of this virus is via direct attack or renal hypoperfusion, inflammatory cytokines, or systemic illness.

Thrombotic Spleen

The thrombotic spleen is a rare complication of this virus and is suspected in those patients who complain about pain in the left side of the abdomen. The patient presented with left side abdominal pain must be evaluated for pulmonary embolism and deep vein thrombosis, including the visceral region of the abdomen [114].

CONCLUSION

SARS-CoV-2 is extremely contagious, and most people in the general community are at risk of

infection. The coronavirus disease (COVID -19) is caused by SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2). The involvement of ACE leads to morbid complications, including respiratory, hepatic, cardiac, renal, and gastrointestinal damage. This brief study will provide a targeted summary of COVID-19-related problems, including hematological, cardiovascular, neurological, gastrointestinal, and other rare complications

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