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Clinical Manifestations of Cytokine Storm and Immune Response to COVID-19: Literature Review

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Abstract

Spreading COVID-19 disease caused by coronavirus 2 causes tremendous health challenges worldwide. Owing to a high transmission rate, fast-spreading disease, asymptomatic carriers, and high infectivity, we observe a pandemic status that we follow today. Although there are different reports of case fatality rates around the globe, the primary determinant of mortality is age. Symptoms of COVID-19 disease vary from asymptomatic individuals to severe acute respiratory distress syndrome (ARDS) and death. The most common complication of COVID-19 is ARDS. Hyperinflammation due to excessive immune response to coronavirus is the leading cause of severe symptoms seen in the course of COVID-19. The virus enters cells utilizing the S1 subunit through the ACE2 receptor. The innate immune response is the primary immune reaction to virus entry. RNA viruses, including coronavirus, replicate in the cytoplasm, assemble, and then exit by exocytosis. Some suggest that SARS-Cov2 uses cell-cell fusion to infect adjacent cells. Different sensors detect the virus particles in the endosomal compartment and cytoplasm, and infected cells induce an immune response to surrounding cells. As a result, the production of cytokines and chemokines such as interferons (INFs) will be augmented. Since coronavirus uses different means to evade the immune system, it is difficult for immune cells to "sense" them; thus, the coronavirus response is not adequate. It has been showing that even a sufficient level of immunoglobulin response couldn't neutralize virus replication. Therefore, the innate immune response is unable to eradicate SARS-Cov2, causes overexpression of cytokines and chemokines that cannot eliminate the virus. Diminished INFs secretion and apoptosis of regulatory T cells (Treg) are the leading cause of dysregulated immune response in a cytokine storm. Inflammatory cells attack infected and uninfected cells, causing more inflammation

and apoptosis of endothelial and epithelial cells. In the end, organ failure occurs due to immune cells' overactivity, cell proliferation, hemorrhage, microthrombi, and remodeling of tissue cells. This review discusses the immune response and pathomechanisms of the associated symptoms in COVID-19.

Keywords

COVID-19, SARS-Cov 2, Clinical Symptoms, Cytokine Storm, Immunological Manifestation

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus (SARS-Cov-2), is spreading rapidly, and the number of cases is still rising around the globe. The emerging of this fast-spreading virus became a challenging health problem worldwide due to the high transmission rate and asymptomatic carriers [1] [2]. Presymptomatic virus shedding is another attribute to further raises the transmission rate [3]. Due to the higher affinity to host cells, the novel coronavirus2 has much more infectivity than SARS-Cov-1 [4]. SARS-Cov-2 transmits by respiratory droplets that may travel 3 - 6 feet [5]. COVID19 symptoms range from asymptomatic individuals to severe acute respiratory distress syndrome (ARDS) and death [6]. The major outbreak of severe acute respiratory syndrome by SARS-Cov1 in 2002-2003 had an overall case-fatality rate of 9.6% [7], and the Middle East respiratory syndrome virus (MERS-Cov) in 2017 had a nearly 36% mortality rate [8]. Although there are different case fatality rates based on age and countries as the virus reached the pandemic, all studies support increased mortality with higher age [9]. The estimated overall case-fatality rate for SARS-Cov-2 is nearly 6% in the USA and differs by country [10].

Based on age and baseline comorbidities, COVID-19 symptoms vary, ranging from asymptomatic individuals to severe organ failure and death [11]. The most common complication seen in patients who were admitted to the hospital was ARDS [12]. The way that the immune system responds to coronavirus defines the course and manifestation of COVID-19. A large body of evidence supports that the etiology of tissue damage is immunopathology rather than direct viral invasion. Overexpression of innate immunity in COVID-19 causes tissue destruction and organ failure and are the most common causes of morbidity and mortality. First described in influenza virus infection, hyper inflammation by cytokine storm [13] causes ARDS, distant organ damage, and failure.

There is a growing need for clinicians to understand the pathomechanism and cause of diverse presentations of COVID-19. This review discusses the immune response to coronavirus and how the host response causes clinical manifestations in the novel COVID-19.

2. Overview of the Human Immune Response to Coronaviruses

SARS-CoV-2 is an enveloped, positive-sense, single-stranded, and non-segmented RNA virus with an 80% genomic composition of SARS-CoV-1 and 96% bat coronavirus [14].

The new coronavirus (SARS-CoV-2) binds to human epithelial cells by its spike protein (glycoprotein S), recognizes angiotensin-converting enzyme 2 (ACE2) receptor on human cells to initiate the first step of infection [15] [16]. Glycoprotein S has two different subunits: S1 contains receptor binding domain interacting with ACE2, and S2, which conveys fusion capabilities to exit endosome into the cytoplasm [15] [17]. Transmembrane proteases of host cells such as transmembrane serine protease 2 (TRMPSS2) activate spike protein and its subunits and enhance coronavirus infectivity [18] [19]. Although ACE2 receptor is expressed in lungs, kidneys, heart, intestine, and testes, well-differentiated nasal epithelia and pneumocytes type 2 serve as the main port of entry and replication of coronavirus in the human body [20] [21] [22] [23] [24].

SARS-Cov-2 has a greater affinity for ACE2 receptors than SARS-Cov-1, although it may enter cells independent of proteases [25]. Furthermore, it has been suggested that SARS-Cov-2 may spread to other cells through cell-cell fusion, explaining the high rate of infectivity and fast-spreading of novel SARS-Cov-2 [4].

After entering the endosome, SARS-CoV-2 fuses to the endosomal membrane and releases its components into the cytoplasm to start replication [16] [26] [27]. SARS-CoV-2 has two different genes encoding structural and non-structural proteins [23]; a few of these proteins antagonize the antiviral activity of infected cells by coronaviruses [28] [29]. Then, the virus assembles all of its components and exits host cells by exocytosis [26].

The presence of coronavirus in the endosomal complex is sensed by toll-like receptors (TLR). However, in the cytoplasm, virus replication components are recognized by CARDs (caspase activation and recruitment domain). In the presence of the virus, both TLRs and CARDs initiate gene transcriptions of type 1 interferons (IFNs), interleukins IL-1, IL-6, tumor necrosis factor (TNF), and other chemokines [30] [31]. Type 1 INF augments immune response against viruses by stimulating macrophages, natural killer cells, CD8 cells, and B cells [32]. By binding of IFNs to their receptors on the same cells or surrounding cells, antiviral gene transcription is enhanced [30] [33] [34]. In addition, IL-6 has a crucial role in balancing immune response during infection; first, by activating plasma cells, Th17, and follicular helper cells. Second, by blocking CD8 cells and cell-mediated response during cytokine storm [35].

Macrophages and dendritic cells are part of innate immunity and work as antigen-presenting cells (APC). They present antigens to T cells to promote acquired immunity and produce different immune-modulatory cytokines to differentiate T cells from various subclasses, such as T-helper 17 [36]. Th17 adjusts

immune response during infection as well as systemic inflammation. Th17 secretes IL-1, IL-6, IL-8, IL-21, TNF-β, and monocyte chemoattractant protein (MCP-1) to enhance acquired immunity [37] [38]. CD4 promotes B cells to produce antibodies and regulates immune response, but cytotoxic CD8 clears the body from the virus. CD4 and CD8 are the most abundant lymphocytes reported in the pulmonary interstitial tissue of infected individuals by SARS-Cov. Thus, CD4 and CD8 activation need a balancing act between the eradication of the virus and overwhelming immune response [39] [40] [41]. APCs enhance IL-12 release by CD4 helper cells that further enhance CD4 helper maturation and stimulate natural killer cells to eradicate the virus [42].

In the persistent phase of infection, humoral immunity plays an essential role in virus eradication. Although antibodies against envelope protein and spike protein of SARS-Cov1 have a neutralizing effect, COVID-19 replication continues after detectable levels of IgG and Ig-M [40] [43] [44] [45]. The complement system is another integral part of innate immunity activated by SARS-Cov19, leading to clinical symptoms driven by complement activity [46]. Host response to coronaviruses is responsible for the majority of symptoms attributed to coronaviruses [7].

Coronaviruses evade the immune system by different means [47]. The coordinated innate immune response is the first step against viral infections, but excessive and disorganized immune responses may contribute to immunopathology [48]. In addition, the natural immune response tends to act more dysregulated by aging [49]. When the immune system cannot mount the adequate adaptive immune response, a persistent reaction from the innate immune system leads to hyperinflammation states such as cytokine storm, ARDS, and ultimately organ failure [50].

3. Cytokine Storm

Cytokine storm is characterized by increased inflammatory markers and multiple organ failure. Infected T cells, and especially CD4, may cause lymphopenia and decrease IFNs production [51]. It has been shown that CD4 numbers may predict viral shedding duration in affected individuals [52]. Infected APCs may cause suboptimal T cells responses leading to excessive immune responses. In this case, host efforts to clear the virus manifests as an immunopathological lethal disease [53]. Coronavirus infection induces dysregulated responses by a dendritic cell such as low-level expression of antiviral cytokines IFN-α and β, moderate up-regulation of pro-inflammatory cytokines TNF and IL-6, and a significant up-regulation of inflammatory chemokines C-C ligands like CCL3, CCL5, CCL2, and C-X-C ligand like CXCL10 [54]. Infected macrophages reveal delayed IFN gene induction [55]. Infected airway epithelial cells produce excessive chemokines CCL3, CCL5, CCL2, and CXCL10 [56].

Well-known factors are causing the extreme immune response to coronaviruses. First is coronaviruses' rapid replication. High replication rates and higher

viral loads enhance the more extensive immune response to infection, manifesting as more severe symptoms [57] [58]. The second is the extension of disease to pneumocytes. Animal studies revealed that immune response to coronavirus is much more extensive when both airway epithelial cells and pneumocytes are infected than when only airway epithelial cells are infected [59]. The third is delayed IFN response due to inhibitory actions of some structural or non-structural proteins encoded by the coronavirus genome. The fast replicating virus hampers INF synthesis, dysregulates monocyte and macrophage response, and subsequently increases T cell apoptosis [48] [51].

Cell destruction is the main aftermath of the extreme immune response. Different studies demonstrate spleen atrophy with necrosis, focal hemorrhages, decreased number of lymphocytes, and increased macrophages' proliferation. The number and size of lymph nodes and the number of CD4 and CD8 in lymphoid tissues may diminish [41] [60]. Due to the accumulation of excessive cytokines, chemokines, and inflammatory cells, apoptosis occurs in endothelial and epithelial cells. INFs and TNF promote apoptosis of tissue cells and compromise microvasculature causing vascular leakage and thrombosis. Organ failure occurs later as tissue damage progress [61] [62]. Another consequence of coronaviruses infection is T cell apoptosis. Decreased number and function of T cells may significantly impair immunoregulation and virus clearance [63]. As an immune response regulator, CD4 loss causes an increased number of macrophages and phagocytosis in the spleen and lungs [64].

Coronavirus hyper inflammation features are lymphopenia plus increased vital markers such as C-reactive protein (CRP), IL-1β, IL-6, IL-2, IL-7, IL-33, TNF-α, IFN-γ, TGF-β, inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), chemokines like CCL2, CCL3, CCL5, C-X-C ligand (CXCL8), CXCL9, CXCL10, granulocyte-colony stimulating factor (G-CSF), procalcitonin, and ferritin [12] [65] [66] [67] [68]. These cytokines and chemokines increase the production, mobilization, and maturation of inflammatory cells in the infection site [69]. Compared to mild cases, fatal cases had significantly elevated biomarkers [66]. IP-10, MCP-3, and interleukin-1 receptor antagonist (IL-1Ra) were independent predictors for the progression of COVID-19 in severe cases [70]. Clinical characteristic analyses found that cytokine storm highly (increased levels of cytokines IL-1β, IL-6, IL-8, IL-10, and TNFα), lymphopenia (decreased CD4+ and CD8+ T lymphocytes), and decreased IFNγ expression in CD4+ T cells are associated with severe presentations in COVID-19 [71]. In a retrospective study of 187 COVID-19 patients, IL-6, IL-10, and serum ferritin were strong discriminators for severe disease [72]. Inflammatory marker elevation leads to hyperinflammation and ARDS and increases mortality in extreme cases [69]. **Table 1** presents the laboratory results from the articles cited in this review.

4. Overview of Clinical Manifestations

Symptoms severity of coronavirus infection depends on airway viral load, age,

Table 1. Summary of the selected papers cited in this review.

Author	Results
Chen, N *et al.*	Neutrophils ↑, IL-6 ↑, CRP ↑, Lymph ↓
Fu, L *et al.*	C.K. ↑, Procalcitonin ↑, Cr ↑, D-dimer ↑, LDH ↑, WBC ↓, Lymph ↓
Henry, BM *et al.*	WBC ↑, Neutrophils ↑, IL-6 ↑, Cr ↑, C.K. ↑, ESR ↑, CRP↑, Ferritin↑, ALT ↑, AST ↑, Lymph ↓, Alb ↓
Huang, C *et al.*	Neutrophils ↑, Procalcitonin ↑, PT ↑, D-dimer ↑, LDH ↑, Alb ↓, Lymph ↓, WBC ↓
Qin, C *et al.*	WBC ↑, Lymph ↓, Procalcitonin ↑, Ferritin ↑, CRP ↑, IL-2R ↑, IL-6 ↑, IL-8 ↑, IL-10 ↑, CD4 ↑, B cell ↑, NK cell ↑, Naïve cell ↑, memory cells ↑, CD28 ↑
Wang, D *et al.*	WBC ↑, Lymph ↓, Neutrophils ↑, Procalcitonin ↑, LDH ↑, D-Dimer ↑, C.K. ↑, Cr ↑, BUN ↑, AST ↑, ALT ↑
Chen, G *et al.*	ALT ↑, LDH ↑, CRP ↑, Ferritin ↑, D-dimer ↑, IL-2R ↑, IL-6 ↑, IL-10 ↑, TNF-α ↑, Lymph ↓, CD4+ ↓, CD8+ ↓

and comorbid conditions [73], although age is the most critical determinant of survival and disease course [9]. Compared to children who have numerous naïve cells ready to respond to new antigens, the number of naïve T cells diminishes over time in the elderly [74]. In animal models of SARS, aged mice had more expressed cytokine and chemokine responses with lower virus clearance and worse outcomes than young ones [75].

The course of presentation in COVID-19 infected individuals can be divided into three phases: initial infection phase, pulmonary phase, and hyper inflammation phase, including ARDS [76].

Most cases are asymptomatic or mild (81%). The most common reported symptoms are flu-like illness including fever (83%), cough (82%), shortness of breath (31%), muscle ache (11%), confusion (9%), headache (8%), sore throat (5%), rhinorrhea (4%), chest pain (2%), diarrhea (2%), and nausea and vomiting (1%) [6] [77]. The average incubation period from contact to the first symptom was 4 days [78]. In a pooled analysis of 181 COVID-19 patients, the first symptoms presented within 14 days after probable exposure in 99% of cases [79]. Analysis of 72314 COVID-19 issues from China revealed that 87% were mild cases defined by no or mild symptoms, 14% were described as severe with significant lung infiltrates or signs of respiratory compromise, and 5% were critical cases of respiratory failure, shock, or multiorgan failure [6].

Although a retrospective study of 201 confirmed COVID-19 Chinese patients, 44 individuals (52.4%) of 84 (41.8%) patients who suffered from ARDS died (11), another retrospective study of 68 fatal cases, 5 patients (7%) died from cardiovascular damage, and 22 patients (33%) died from both respiratory failure and cardiovascular damage [11] [66]. Many studies demonstrated that age and baseline comorbidities are associated with increased risk of severe complications such as ARDS, kidney injury, ICU admission, and death. A vast body of evidence suggests that elevated biomarkers and inflammatory indexes are correlated with increased severity and death rate through the course of disease [11] [12] [80]. A

severe manifestation usually occurred in 8 - 14 days after the first symptoms, the median time of death within 6 - 19 days after the illness onset, and discharge time was around 3 weeks on average [66] [81] [82] [83]. **Figure 1** depicts the immune response to the coronaviruses. The consequences of immunopathologic response showed in red.

5. Pulmonary Involvement

We learned from severe acute respiratory syndrome (SARS) that the initial phase of Coronaviridae infection is pulmonary epithelial cell proliferation with innate immune response mediated by macrophages and monocytes [84].

The pulmonary phase proceeds to further lung injury by vasodilation and endothelial permeability due to leukocyte recruitment. Despite diminished viral load, in this phase, hypoxemia and cardiac stress progress further, proportionate to the extent of lung injury [58] [76]. Simultaneous with the decreased viral burden, pulmonary symptoms worsen 1 - 2 weeks after initial respiratory symptoms [85].

Diffuse alveolar damage (DAD) is the leading histological feature in lung injury. DAD pathology reveals lung consolidation and edema with pleural effusions and focal hemorrhages with infiltration of neutrophils and macrophages. The viral antigen is detected in vascular and respiratory endothelium, macrophages, lymphocytes, and monocytes [86]. Autopsy of fatal cases revealed fibrin microthrombi and micro infarct [41] [87]. Focal desquamation of alveolar epithelial cells and proliferation of type II pneumocytes were also reported [41]. Prolonged prothrombin time (PT), elevated D-dimer, and activated partial thromboplastin time (APTT) has been reported in hospitalized COVID-19 cases [71] [81] [83]. Despite increased white blood cells and neutrophilia, lymphopenia is a grave sign of disease progression to ARDS in patients with critical conditions [12] [71]. SARS-Cov infection, a virus from the same family of COVID-19 virus, infects lymphocytes and, as a result, decreases both CD4 and CD8 till the end of recovery. T regulatory cells maintain homeostasis of the immune response during infection and recovery to prevent excess immune response, and in SARS-Cov-2, the number of regulatory and helper T cells is decreased [86] [88] [89]. Older age, hypertension, diabetes, high fever, lymphopenia, injury to other organs, and elevated D-dimer and inflammatory markers are predictors of ARDS. Advanced age, neutropenia, elevated D-dimer, and inflammation is associated with higher mortality in those with ARDS among all risk factors [11].

Soluble ACE 2 in blood has a protective role in heart failure and respiratory failure [90]. Tumor necrosis factor-α convertase (ADAM17) has cleavage activity on ACE 2 receptors and releases soluble ACE 2 [91]. Administration of soluble ACE 2 had a favorable result in ARDS and lung injury [90] [92]. It's still unclear if the use of ADAMS17 could be protective against viral entry in ARDS associated with SARS-Cov 2. However, a new study reported that recombinant Human ACE 2 (hrsACE2) could significantly block early SARS-CoV-2 infections on engineered human cells infected by SARS-Cov 2 [93].

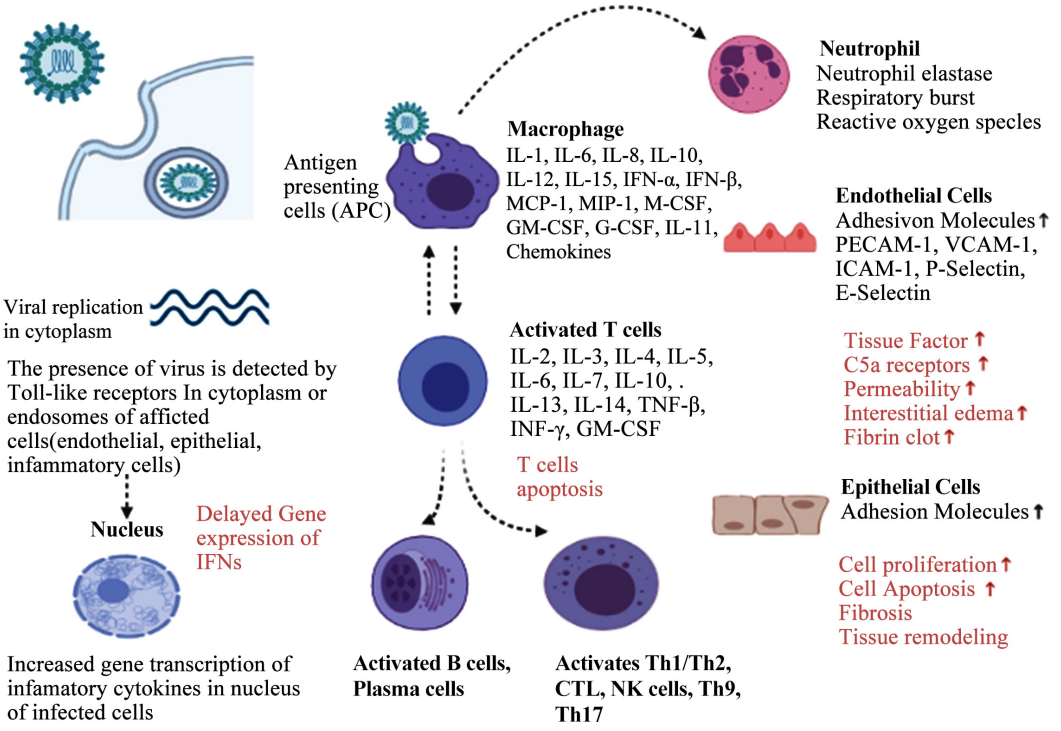

Figure 1. Consequences of extreme immune response to coronaviruses. Created with BioRender.com.

Despite diminishing viral loads, some patients may suffer from distant organ injury with excessive immune response. Distant Organ injury without virus infiltration shows the role of Systemic inflammation in distant organ failure [41].

6. Radiologic Findings

Bilateral pulmonary infiltrations were more common than unilateral infiltration (95% vs. 5%) [11]. Bilateral reticulonodular opacities (52.4%), ground-glass opacities (47.6%), pleural effusion (28.6%), peribronchial thickening (23.8%), focal consolidation (19%), pulmonary edema (9.5%), venous congestion (4.8%), atelectasis (4.8%), and clear chest x-ray (4.8%) [94] are the most common findings in patients who were admitted due to COVID-19. Ground-glass opacities (80.0%) and bilateral pneumonia (73.2%) were the most common findings on chest CT scans [78].

7. Cardiovascular Involvement

The rate of cardiac injury among different studies was variable from 7% to 18% in hospitalized cases [12] [81] [82] [83]. Cardiac injury is the independent risk of mortality along with lung injury [82]. Mortality was 51.2% in cases with cardiac injury versus 4.5% of patients without cardiac injury [82]. Initial cardiac injury with elevated troponin has been reported with no lung injury [95] [96]. COVID-19 associated heart failure was 23% among all the patients and 58% among fatal cases [83]. ACE 2 receptor, the port of entry for SARS-Cov 2, basically regulates heart function, and in an animal study, mice with dysfunctional ACE 2 receptors

developed left ventricular failure [97]. SARS-Cov infection downregulates heart ACE 2 receptors, theoretically enhancing heart dysfunction [98]. Severe cases of COVID-19 had a higher level of troponin I and brain natriuretic peptide (BNP) [66] [94]. Equally important, there is a correlation between cardiac enzyme levels and prognosis and mortality rate in patients with SARS-Cov 2 infection [83]. Among all mortality factors in COVID 19 patients, cardiac injury has a more significant weight [81] [82].

The cardiac injury mechanism is not precise, but a combination of direct viral infiltration, systemic inflammation, hypoxia, and cardiac stress is plausible. Like SARS-Cov1, SARS-Cov 2 viral inclusions have been seen in the myocardium and cardiac vasculature [98] [99]. Animal studies show that IL-6 and TNF can cause systolic dysfunction [100] [101]. Mitochondrial dysfunction may lead to cardiac dysfunction in septicemia [102]. Cleavage of ACE 2 receptors by TNF α convertase (ADAMS-17) may decrease local membrane ACE 2 and play a protective role against the virus entry. Soluble ACE 2 may diminish ACE 2 receptors and reduce the risk of heart dysfunction, although it may act as a compensatory mechanism in heart failure [103] [104]. Pericytes have the highest number of ACE 2 receptors in the heart, and their dysfunction disrupts microcirculation, causing ischemia [105]. ACE 2 interacts with inflammatory cells, including macrophages, to reduce inflammation; thus, lower angiotensin 2 levels have pro-inflammatory effects [106] [107]. Study shows that macrophages and CD4 cells myocardial infiltration in SARS-Cov1 were detected in 35% human heart autopsy samples [98]. The significant risk factors associated with elevated troponin are age, male gender, and associated comorbidities such as hypertension. In addition, elevated troponin was associated with an increased risk of ARDS, kidney injury arrhythmia, and coagulopathy [81].

Blood pressure and heart rhythm abnormalities are frequently seen in critically ill SARS-Cov 2 patients. However, it's not clear whether blood pressure changes are due to ACE 2 receptor or vagoplegic status in critically ill patients [66] [71].

Although one study shows different arrhythmias from tachycardia and bradycardia to asystole is prevalent in 16.7% - 44.4% of severe ICU cases [12], another study reported 5.9% ventricular tachycardia and fibrillation [81]. In addition, patients with pneumonia have a higher risk of cardiovascular events [108]. Presumably, acute myocardial events risk factors in COVID-19 patients are platelet, endothelial cells, and macrophage activation associated with hyperinflammation.

A systemic infection such as influenza may activate the immune system and inflammatory cytokine cascade. Study shows that local arterial inflammation may activate inflammatory cells in atheroma, leading to plaque rupture [109] [110]. Vasoconstriction may also occur with the activation of vascular endothelial cells due to inflammation [111]. The D-Dimer level was significantly increased in COVID-19 cases, showing that hypercoagulability state may lead to myocardial injury or vasculature thrombosis [112].

8. Renal Involvement

Overall, 40% of COVID-19 cases have abnormal kidney function [80], and kidney injury may occur in 0.5% to 15% of cases. Both virus proliferation and hyper inflammation may contribute to kidney injury of COVID-19 patients [80]. Kidney injury incidence was significantly higher in males, older patients with comorbidities such as hypertension and chronic kidney disease. Fatal hospitalized cases had a significantly higher rate of kidney injury that is more common in Patients with higher leukocyte count and procalcitonin levels (69). Although the urinary system, including the kidney, has a very high ACE 2 receptor expression, microscopic examination of SARS patients did not show any electron-dense deposits [113] [114]. However, in COVID-19 patients with nephropathies, SARS-cov2 induced cytoplasmic renal tubular inclusions [115]. Cytokine storm and systemic inflammatory response cause endothelial dysfunction and thrombosis, causing microangiopathies [116]. Injured renal tubular cells upregulated the IL-6 that has a key role in cytokine storm [11]. Since COVID-19 patients have increased creatinine kinase due to hypoxia and shock, thus rhabdomyolysis may contribute to kidney injury [12].

9. Hepatic Involvement

The elevated liver enzyme was a common finding in nearly 21% - 37% of COVID-19 cases [6] [83], and liver failure defined as high liver enzyme > 3 times of standard limit reported in 48% - 62% fatal cases [94]. Although ACE 2 receptors present in cholangiocytes, they do not exist on hepatocytes, Kupffer cells, and endothelial cells [117]. Because of the average level of alkaline phosphates in COVID-19 patients, there should be another mechanism for liver injury by SARS-Cov 2. Hypoxemia and shock are the possible liver injury etiologies in COVID-19 patients [118]. Studies showed the correlation between Lymphopenia and C-reactive protein and liver injury in patients with COVID-19 [119]. In addition, viral RNA was detected in the liver in post mortem studies showing mild lobular lymphocytic infiltration with focal macrovesicular steatosis and mild sinusoidal dilatation [120].

10. Thrombosis

Systemic infection may be complicated with coagulation dysfunction mediated by cytokines leading to multiple organ failure [121]. Inflammatory cytokines such as TNF-α, IL-1α, IL-1β, IL-6, IL-8, leukemia inhibitory factor, IFN-γ, and monocyte chemoattractant protein 1 (MCP-1) in addition to endothelial injury, activate tissue factor and enhance prothrombotic state [122] [123] [124]. Infection may activate platelets, enhancing coagulation [125]. Post mortem reports of fatal cases of ARDS due to SARS-Cov 1 revealed pulmonary vascular thrombosis [99]. IL-1β and IL-6 promote the expression of adhesion molecules on endothelial cells leading to inflammatory cell infiltration and vascular inflammation. Indeed, cellular damage and local viral proliferation enhance endothelial dys-

function and microthrombi further [126] [127]. The localized macrophages can also release pro-coagulant factors such as plasminogen activators, secreted by macrophages angiotensin II, enhancing a prothrombotic state manifested by the microthrombi formation in several organs.

11. Nervous System Involvement

Several studies reported neurologic involvement by coronaviruses. Coronaviruses infected the brain could cause polyneuropathy, encephalitis, and ischemic stroke [128]. Infection-induced encephalopathy may present as cerebral edema without evidence of inflammation in cerebrospinal fluid analysis. Patients may develop headaches, dysphoria, mental illnesses, and delirium. Disorientation, loss of consciousness, coma, and paralysis may occur in severe cases [129]. Nearly 20% of patients infected by MERS-Cov exhibited neurologic complications that appeared approximately 2 - 3 weeks after resolving respiratory symptoms. Ranging from neuropathies to encephalitis, symptoms varied from hyperesthesia, toxic and infectious neuropathies, intensive-care-unit-acquired weakness, and Bickerstaff's encephalitis overlapping with Guillain-Barré syndrome [130]. As well in Post-mortem reports of SARS-CoV cases, infiltration of monocytes and lymphocytes in the vessels, demyelination of nerve fibers, ischemic changes of neurons, and virus particles were noted [86]. Brain Biopsy of Patients with multiple sclerosis(MS) showed that Human coronaHCOV viruses particles in tissues [131] [132]. Nearly 50% of patients with MS had RNA of HcoV-Oc43 in their CSF [133]. It appeared that activated T cells in These patients were hyper-reactive to myelin as well as the virus 16. Few patients have new reports of Miller Fisher syndrome, a variant of Guillain-Barré syndrome, and polyneuritis cranialis in COVID-19 patients [134]. About 36.5% of COVID-19 patients may develop neurological symptoms and more commonly seen in patients with severe symptoms. Both central and peripheral nervous systems may be involved. Headache, paresthesia, loss of consciousness, hypogeusia, anosmia, and seizures are among the most prevalent symptoms [135]. Approximately 33.9% of Patients with CoVID-19 reported olfactory or taste involvement, with 18.6% reported both [136]. Studies defined coronaviruses probably gaining access to the CNS by At least 3 routes, including the olfactory nerve, a hematogenous route, and lymphatic systems [137] [138]. Infected macrophages circulating in the blood throughout the body may contribute to direct nervous system invasion. Coronaviruses infect macrophages, microglia, and astrocytes in CNS and infected. Glial cells may secrete numerous inflammatory cytokines such as IL-6, IL-12, IL-15, and TNF-α [139]. CNS infection with SARS-CoV 2 activates CD4+, which induces the macrophages to secrete interleukin-6 (IL6) [140]. Sparse perivascular and leptomeningeal infiltrates of CD3+ T lymphocytes in COVID-19 brains, similarly encountered in sepsis or systemic inflammation [140]. Increased permeability of the blood-brain barrier by hyperinflammation facilitating more cytokines entry and viral invasion is another possibility [141] [142]. SARS-Cov in-

volves Brain tissue through attachment to the endothelial lining of the blood-brain barrier and brain vessels. SARS-Cov enters the brain cells by virus budding during replication as well 50. Vascular Endothelial damage by viral replication results in vascular rupture and may cause cerebral hemorrhage and death seen in a patient with COVID-19 [143] [144] [145]. The olfactory nerve has been suggested as one of the neuronal portal entries of respiratory viruses, including coronaviruses [145] [146]. Direct Viral entry to the nervous system occurs through the cribriform plate or olfactory bulb by trans-synaptic route [138] [147] [148] [149]. There are reports of encephalitis with detection of viral RNA in cerebrospinal fluid with the possibility of direct central nervous system invasion by SARS-Cov2 [150] [151]. Post mortem studies of COVID-19 cases showed lymphocytic endotheliitis (endothelialitis) in vessels and Lymphatic drainage of in internal organs such as heart, kidney, lung, liver, the small intestine and brain. Endothelialitis causes vascular dysfunction that leads to organ ischemia, tissue edema, and a prothrombic state due to vasoconstriction and associated inflammation [152] [153].

Mice infected with SARS-Cov had brain involvement that was more prominent in the brain stem and thalamus area, cardiopulmonary regulation, and it may play a role in cardiopulmonary compromise in COVID-19 patients [154] [155]. SARS-Cov downregulates replication of ACE protein in infected cells of organs like the brain. Decreased level of ACE leads to the insensitivity of baroreceptors and fluctuation of heart rates and blood pressure and, in addition to sympathetic overactivity, result in blood pressure elevation and cardiac dysfunction [156].

Another cause of brain damage in patients with COVID-19 is toxic encephalopathy caused by Severe hypoxia and viremia [137]. Subsequent brain injury ensues with further hypoxemia, which causes brain edema and intracranial hypertension with deterioration of brain function [157]. Cytokine storm during lung injury, hypoxemia, and sympathetic overactivity leads to CNS hyperactivity which might play a crucial role in the pathogenesis of neurogenic pulmonary edema (NPE), result of neurologic insult, and which finally deteriorate respiratory and cardiovascular function in COVID-19 patients [158] [159].

Increased D-dimer and platelet has been reported frequently in a cytokine storm, showing the propensity to hypercoagulation and cerebrovascular accident in COVID-19 [94] [160]. Nearly 5% of COVID-19 patients developed signs of cerebrovascular accidents, which was more common in patients with older age, cardiovascular risk factors, and higher C-reactive protein and D-dimer [135] [161].

12. Conclusion

Inadequate adaptive immune response leads to immune dysregulation, destroying infected and uninfected cells. Hyper inflammation and apoptosis of endothelial and epithelial cells lead to organ failure due to immune cells' overactivity.

Cell proliferation, hemorrhage, microthrombi, and tissue remodeling are all consequent, making the symptoms we on\bserve with SARS-Cov 2 infection.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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