

Multi-organ Dysfunction Due to SARS-CoV-2 Infection: A Comparative Overview

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Abstract: SARS-CoV-2 or COVID-19 is a highly transmittable and pathogenic viral disease, which was first reported in the province Wuhan of China in late December 2019. The disease has shown its catastrophic effect in more than 200 countries and territories, causing more than 53.7 million confirmed cases and over 1.3 million deaths since its outbreak. Although the virus was primarily presumed to cause respiratory disease, reports are emerging of the plausible impact of the virus on multiple organs. The multi-organ dysfunction in severe patients of COVID-19 results in high morbidity and mortality rate compared to the other coronavirus family members like SARS and MERS. In this review, we provided a brief overview of the current insights of potential COVID-19 impacts on multiple organ functions. Reports suggest that the virus may exert direct (e.g., using ACE2 receptor) or indirect (e.g., cytokine storm) effects on several organs, including the lung, kidney, heart, liver, and brain. These multi-organ injuries may contribute to poor health outcomes and even may lead to death, especially to those suffering from cardiac disease, diabetes, liver, kidney diseases, etc. However, further investigation is required to know the exact mechanism of the infection. This study will provide valuable information on multi-organ dysfunction due to COVID-19 and thus, help clinicians to combat the disease until an effective vaccine arrives.

Keywords: SARS-CoV-2, Pandemic, Multi-Organ Failure, Angiotensin-Converting Enzyme 2 (ACE2), Cytokine Storm

1. Introduction

At the end of December 2019, the primary reports of the viral disease stood out when a group of patients with pneumonia was seen in Wuhan, the capital of Hubei, China. Genetic evidence proves that they are hiding out in nature especially in animals, possibly for decades, and obtained the power to infect humans by a genetic mutation. Several characteristics are required to declare a pandemic situation such as a unique type of infection, which covers huge geographical regions, and has excessive attack rates, etc. [1]. Swine flu, Influenza, Spanish flu, Cholera, and Bubonic plague are the major pandemics that occur in previous human history. On February 11, The International Committee on Taxonomy of Viruses has renamed the virus as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and WHO officially named and declared COVID-19 as pandemic

later on March 11, 2020 [2]. The National Health Commission of China provides information about the novel coronavirus that had more than 95% sequence similarities with the bat coronavirus and more than 70% similarities with the previous SARS-CoV [3]. However, the earlier cases indicated bat as the primary reservoir for the Covid-19 virus emerging from the live animal market which then quickly transmitted via human to human contact [4].

SARS-CoV-2 can bind with the alveolar pneumocytes, where Angiotensin Converting Enzyme 2 (ACE2) is expressed greatly. SARS-CoV-2 can readily attack cells at multiple points of the host (lung and throat being the primary target), which is different from other classes of this virus [5]. Apart from causing pulmonary disease, SARS-CoV-2 has the potentiality to infect other organs of the human body as ACE2 expresses in nearly all the organs. Though it is not clear that how SARS-CoV-2 spread into several organs,

some predicted pathways have been deduced by researchers. In this context, we are focusing to find out and co-relate the mechanisms by which SARS-CoV-2 infects.

The COVID-19 virus started to show its catastrophic impact on 2020 by emerging globally. In total 53,732,556 confirmed cases were recorded worldwide including 1,308,572 deaths (2.44% of total infected cases) by WHO till 14th November 2020 (Table 1). According to WHO, COVID-19 becomes severe to those with a compromised immune system and have other health complications like cardiac disease, diabetes, liver, and kidney diseases. To control the pandemic situation, the WHO provides accurate information and statistics to help countries to prepare and respond against the virus. Despite the low death rate, the fast and rapid transmission of Covid-19 makes it a serious concern for everyone.

2. Virology

Coronaviruses are enveloped positive-sense single-stranded RNA viruses ranging from 80-220nm in diameter with a crown-like spike which is 20 nm in diameter [The structure of SARS-CoV-2 has been discussed in Figure 1]. Coronaviruses are members of the subfamily *coronavirinae* in the family *coronaviridae*. The subfamily of CoVs is genotypically divided into four genera: α , β , γ , and δ CoVs. α and β -CoVs mainly cause infections in humans. SARS-CoV-2 as well as SARS-CoV and MERS-CoV are part of these β -CoV genera. SARS-CoV-2 has a zoonotic origin and bats are accounted for the best reservoirs for zoonotic viruses. Until now, it stays conflicting concerning the cause of SARS-CoV-2, and etiologic examinations are being led by Chinese health authorities. Phylogenetic research indicates that SARS-CoV has 79.5% and MERS-CoV has a 50% sequence identity with SARS-CoV-2. Similar to other β -CoVs, the genome size of SARS-CoV-2 virion is 29.9 kb and the SARS-CoV-2 S protein has a full size of 1,273 amino acids [6–8]. The nucleotide sequence of spike (S) protein of SARS-CoV-2 (which mainly interacts with host cell receptors) shares 72% sequence similarity with SARS-CoV. The SARS-CoV-2 virion has a nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid (N) protein. Gene order of SARS-CoV-2 is 5'-replicase ORF1ab-S-envelope (E)-membrane-(M)-N-3'. The nucleocapsid is made with phospholipid bilayers and enclosed by two different types of spike proteins: the spike glycoprotein trimmer (S), and the hemagglutinin-esterase (HE). In the viral envelope, the membrane (M) protein and the envelope (E) protein are found within the S proteins. Almost 15,018 mutations were observed by China National Center for Bioinformation. The 21kb sized ORF1ab gene contains 16 predicted non-structural proteins, several downstream ORF like other SARS-CoV. Feasibly the polybasic (furin) cleavage site insertion at the junction of the S1 and S2 subunit of the S protein increases the infectivity of the virus [9]. Most of these non-structural proteins of SARS-CoV-2 show more than 85% sequence similarities with SARS-CoV; except for

the accessory gene ORF8 of SARS-CoV-2, encoding a novel protein (shows only 40% sequence similarities). Interestingly, a 382-nucleotide deletion covering the whole ORF8 of SARS-CoV-2 has been discovered during a genomic study in Singapore. This sort of deletion might illustrate how does the virus adapt in humans while transmitting from an animal host [8].

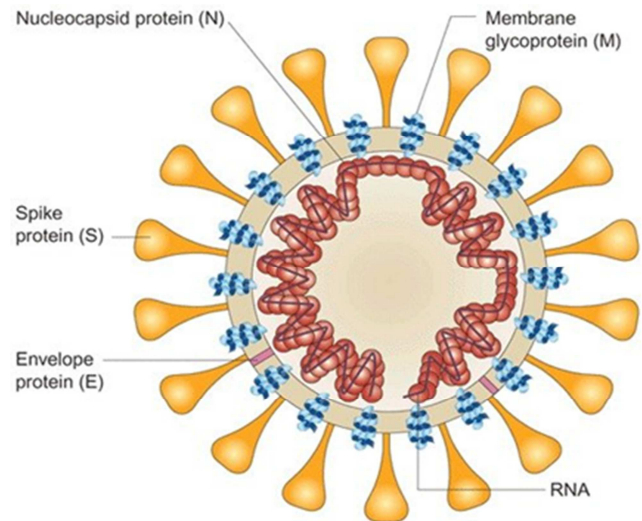


Figure 1. Structure of the SARS-CoV-2. SARS-CoV-2 is an enveloped, positive-sense-single-stranded RNA virus. The viral surface proteins (spike, envelope, and membrane) are immersed in a lipid bilayer envelope derived from the host cell. The nucleocapsid protein covers the ssRNA of the virus [10].

3. Pathogenicity

Novel coronavirus can spread via fecal-oral transmission along with respiratory droplets [11]. A significant amount of coronavirus patients experiences severe diarrhea, nausea, vomiting, and abdominal discomfort due to the accumulation of the virus in the lungs and affecting other organs as well. Scientists also find a detectable amount of viral RNA in the fecal samples [12]. Respiratory droplets of an infected person may infect other people coming in contact within a range of three to six feet. According to the type of surface, temperature, and humidity of any environment, coronavirus may persist on a surface from a few hours to several days [13, 14]. The virus mostly affects the alveolar cells of the respiratory system [15].

The surface of SARS-CoV-2 has a series of spike proteins that look like a crown under an electron microscope and thus give rise to the name corona [6]. The spike proteins allow the entry of the virus into the host cell by attaching to the membrane of the cell through a specific binding receptor called “The Angiotensin-Converting-Enzyme 2 (ACE2)”. ACE2 is expressed in the lung, heart, kidney, and intestine and also in the bile duct [14, 15]. The spike protein of the virus has two subunits in it, a) S1, which mainly binds to the host cell receptor, and b) S2 which mediates the fusion of the viral and cellular membranes. The virus mostly attacks type-2 pneumocytes through its spike protein via the ACE2 receptor.

The virus gets into the cell by endocytosis. As soon as it gets into the cell, it releases its ssRNA molecule. Eventually, the RNA molecule takes over the host cell ribosome and start producing different protein molecules of it. It also utilizes the RNA-dependent RNA polymerase enzyme to synthesize its genome RNA. As coronavirus damages type-2 pneumocytes, it can secrete numerous cytokines and inflammatory products [16]. This activates alveolar macrophages, which then releases specific Interleukin-1, Interleukin-6, and tumor necrosis factor (TNF). These molecules come into the capillaries surrounding the alveoli and cause capillaries smooth muscle relaxation [17]. They are also responsible for endothelial cell contraction and relaxation. All these events finally lead to vasodilation and increase capillary permeability. Besides, loss of surfactant due to damage to type-2 pneumocytes, resulting in increased surface tension, and eventually, alveoli collapse [18].

The collapsed alveoli may decrease the gas exchange, which will cause hypoxia (a decrease of the oxygen concentration in the blood along with trouble in breathing). Increased inflammatory cytokines will attract neutrophils that can release reactive oxygen species and other proteases to kill the virus or virus-infected cell. At the same time, these oxygen species and proteases can damage the surrounding type 1 and type 2 pneumocytes and thus reducing the gas exchange and mechanical irritation leading to cough. IL-1 and IL-6 can then be traveled into the hypothalamus and stimulate it to release specific prostaglandins that increase the

body temperature resulting in fever [19].

Again, the low partial pressure of oxygen can stimulate the chemoreceptors and these receptors would stimulate the sympathetic system. The heart will try to pump more and more blood to make the oxygen demand and the heart rate will increase consequently. On the other hand, the respiratory rate will also increase as the body need more oxygen to inhale and exhale more carbon dioxide [20, 21]. Mortality rate increases due to COVID-19 with patients suffering from heart disease, asthma, diabetes, chronic respiratory disease, cancer, and hypertension. These conditions make both the innate and adaptive immune systems vulnerable to fight against the disease and may lead to multi-organ failure [14, 15, 22].

4. Worldwide Perspective

As of 14th November 2020, the WHO reported over 53.7 million confirmed COVID-19 cases including more than 1.3 million deaths worldwide, and 216 countries and territories are affected by the virus (Table 1). Among the reported COVID-19 cases, the Asian continent has a higher recovery rate whereas Europe has a higher number of active cases compared to other continents. Furthermore, case fatality rates (CFR) across continents due to COVID-19 are currently South America (3.0%), North America (2.9%), Africa (2.4%), Oceania (2.4%), Europe (2.3%), and Asia (1.8%) respectively.

Table 1. Worldwide COVID-19 Scenario.

Continents	Total Cases	Total Deaths	Total Recovered	Active Cases	Total Population	Population Density/km ²
Asia	14,904,676	263,281	13,295,832	1,345,563	~4.6 Billion	150
Africa	1,961,099	46,906	1,650,737	263,456	~1.3 Billion	45
Europe	13,484,610	315,654	4,977,740	8,191,216	~747 Million	34
North America	13,067,017	373,630	8,291,984	4,401,403	~369 Million	20
Oceania	42,088	994	32,882	8,212	~42 Million	5
South America	10,272,345	308,092	9,264,333	699,920	~655 Million	32
In Total	53,732,556	1,308,572	37,514,167	14,909,817		

Source: WHO, Worldometer (<https://www.worldometers.info/coronavirus/>); Last Updated: 14/11/2020 at 11:59 pm

The actual number of infected cases is suspected to be higher than documented and expected to be nearly 10% of the world's population. The possible reasons behind undocumented reports might be asymptomatic infections that are not tested, a limited number of testing facilities, particularly in developing countries. Apart from the differences in mortality rates, the countries and territories can be attributed to considerable heterogeneity in virus dissemination, variability in infection fatality rate (IFR), and erroneous counting of deaths [23]. Besides, risk factors for severe COVID-19 are considered to be old age and underlying health issues, such as cardiovascular disease, diabetes, chronic kidney disease, etc., which may differ in population across different countries [24, 23]. In a recent study, Clark et al. (2020) suggested that about 1.7 (range 1.0-2.4) billion people, 22% (range 15-28) of the global population, have at least one underlying disease that could increase their risk to COVID-19 [24]. Although this is a

massive figure, the consequence would likely ensue if substantial interventions such as effective and safe vaccines are not available faster for preventing the further spread of the infection [23].

While some countries worldwide have succeeded in the containment of the epidemic, others are still dealing with the first wave with the steady rise and decline of regular cases and deaths [25]. Epidemiologists indicated that a stronger second wave of COVID-19 pandemic is likely to occur before the end of 2020. Future waves of the pandemic may vary geographically, and their severity is likely to depend on the efficacy of local control policies [23]. Researchers are speculating that the COVID-19 pandemic may exist for a few more years and maybe slowed down if the majority of the world's population (more than 60%) develops herd immunity from the infection either naturally or by vaccination [26, 27]. The herd immunity threshold depends mainly on the basic reproduction number (R_0) of an infection [27]. Although the

exact R0 value for COVID-19 is very hard to determine, as many asymptomatic cases were not accounted for at this stage. An estimated R0 value of 2.5 (range: 1.8-3.6) is suggested for SARS-CoV-2 recently, which was quite similar compared to the R0 value (range: 2.0-3.0) of SARS-CoV [8]. Considering the estimated value of R0 for SARS-CoV-2, the threshold for herd immunity would be approximately 60%; which implies that to achieve herd immunity, about 60% of the world's population must be infected with the virus [23, 27]. Without vaccination, achieving herd immunity naturally is considered theoretically possible if the rapidly evolving infection tends to span a few more years and is not strictly controlled [27]. However, this would be catastrophic as millions would succumb to the disease, and many susceptible individuals will die [23]. Therefore, for long-term prevention and control of this current pandemic and its future spread, effective and safe vaccinations are the most efficient method, and widespread vaccinations of the population globally, particularly of the susceptible individuals, should be conducted faster. To date, no commercially approved vaccines for COVID-19 have been available, although certain vaccines are in phase II human clinical trials and others have progressed to phase III (e.g., Sputnik V, ChAdOx1, CanSino, etc.) [8].

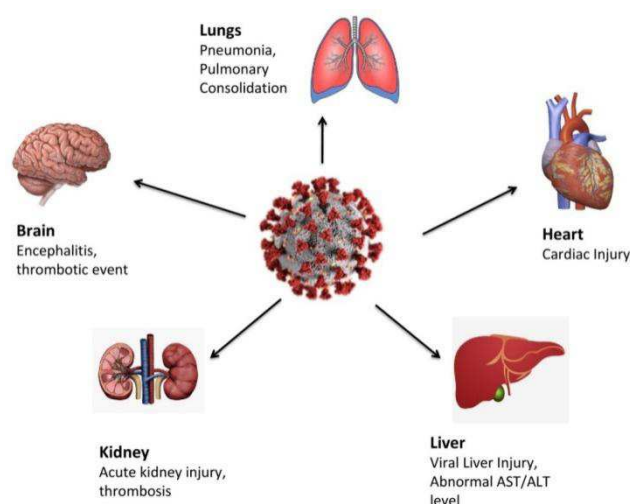


Figure 2. Graphical representation of the impact of SARS-CoV-2 on different organs. Studies suggested that Lung, Heart, Liver, Brain, Kidney, etc. could be damaged due to the infection of SARS-CoV-2.

5. Multi-organ Dysfunction by SARS-CoV-2

5.1. Lung Injury

Researchers divided human COVID-19 into two categories. Low pathogenic COVID-19 infects the upper respiratory tract and Highly pathogenic COVID-19 can infect the lower respiratory tract causing severe acute respiratory syndrome [28]. In most COVID-19 patients, computed tomography (CT) scans demonstrate ground-glass opacity (GGO), crazy-paving pattern, consolidation, and traction

bronchiectasis, and in some observations, pleural effusion and lymphadenopathy were found [29–32]. Continuous CT image follow-up in affected patients indicated that COVID-19 pneumonia in the lung gradually develops from focal unilateral to diffuse bilateral ground-glass opacification, predominantly in the lower lobes, and which may contribute to the further progression of crazy-paving pattern and subsequent consolidation [29, 31]. Being highly opportunistic pathogens, COVID-19 may attack the lower respiratory tract and result in severe complications, like pneumonia, exacerbations of asthma, bronchitis, bronchiolitis, and respiratory distress syndrome [33]. Besides, in the hospital settings, patients can be categorized into two distinct phenotypes respectively “Type L” and “Type H”, considering the lung mechanics and respiratory distress as well as monitoring CT scans. “Type L” patients can be identified by poor lung elasticity, decreased lung weight, and a low response to positive end-expiratory pressure (PEEP) and may not specifically have dyspnea. The “type H” patients, by contrast, demonstrate considerable consolidation of CT, high lung elasticity, increased lung weight, and high PEEP responses, which display the properties of acute respiratory distress syndrome (ARDS). These conceptual methods might help to comprehend the severity and extent of COVID-19, and also the management of different therapeutic interventions and ventilatory strategies depending on the underlying physiology to alter the outcome of patients [34, 35]. Furthermore, histopathology of the lungs revealed predominant exudative and proliferative diffuse alveolar damage (DAD) including widespread capillary congestion, discrete hyaline membranes, pneumocytes depletion, edema, and pulmonary embolism [36, 37].

Severe lung injury can be caused by two reasons: One, viral infection, and another is immune overactivation. COVID-19 binds with the ACE2 receptor of the lungs thus downregulates its expression. This increases lung edema which leads to ALI/ARDS [16]. Cytokine storm- a large replication of the virus in respiratory epithelial cells equipped with by COVID-19 infection stimulate acute inflammation and severe respiratory disease. After infection into lung tissues, COVID-19 activates dendritic cells and macrophages that further produce pro-inflammatory cytokines such as IL-12, IL-15, and IL-18. Interaction between these cytokines leads to the chemotaxis and activation of natural killer (NK) cells, Type 1 helper T (Th1) cells. They release granulocyte - macrophage colony - stimulating factor (GM - CSF) and interleukin - 6 (IL - 6), IFN- γ , TNF- α , IL-1, IL-2 which results in a cytokine storm. Activated NK cells secrete granzymes, nitric oxide (NO), reactive oxygen species (ROS), perforin, and cytotoxic T lymphocytes to kill the virus. An excess amount of inflammatory molecules damages the epithelium and endothelium line and causing alveolar damage and limits gas exchange which causes pneumonia [16, 38].

Also, blood abnormalities, together with the low quantity of lymphocytes, hypoalbuminemia, high level of lactate dehydrogenase (LDH), low level of neutrophils, C-reactive

protein (CRP), and Angiotensin II were related to the severe lung injury [3]. When pulmonary fibrosis caused by COVID-19 develops severe respiratory failure, professionals perform lung transplantation as a last step medication with strict precaution. But before LT several factors should be in concern- despite maximum medical support, irreversibility of refractory respiratory failure, positive-turned-negative virology, absence of other organ dysfunction, etc. [39].

5.2. Effects on Heart

A recent study has found that Covid-19 can cause multi-organ failure though it primarily affects lungs by causing interstitial pneumonitis [40]. Patients with hypertension, coronary heart disease, diabetes, kidney disease, and immunosuppressive diseases are said to be at higher risk for the mortality and morbidity of the disease. The elder people are at greater risk in terms of COVID-19 mortality comparing to the younger ones [17, 20, 41, 42]. Patients with pre-existing cardiovascular disease (especially hypertension) had the highest morbidity rate amongst the other complications. A recent study based on 5,000 patients in New York City, found that people with hypertension (57%), obesity (40%), and diabetes (34%) were co-morbid [40]. Another analysis among 72,314 COVID-19 patients from the Chinese Centre for Disease Control and Prevention reported that 13% had Hypertension, 5% had diabetes and 4% had known cardiovascular diseases. Among them, 40% of patients with hypertension, 20% of patients with diabetes, and 22% of patients with pre-existing cardiovascular diseases did not survive [41]. Different published reports from medRxiv, bioRxiv suggested the detailed evidence of myocardial injury in 20-40% of hospitalized patients such as cardiac pain, cardiac arrhythmias, coronary failure, and cardiac death [40]. Interestingly, it is also evident that COVID-19 may lead to heart disease even in people without having pre-existing cardiovascular diseases [20].

5.2.1. Hypertension and COVID-19

Though it is still not clear if hypertension works as a risk factor for COVID-19 or not. However, several studies and available data suggested that it is more prevalent in patients with severe conditions. A study among 44,672 patients in China CDC reported that hypertension was common in 12.8% and 39.7% were eventually died [17, 40]. It is also reported that hypertension increased the odds ratio (OR) for death in COVID-19 patients and it is more frequent in older people and they have a higher mortality rate than younger people [40].

5.2.2. Cardiac Arrhythmia and COVID-19

Viral infections are said to be interlinked with myocardial inflammation, activation of the sympathetic nervous system, and metabolic dysfunction; together they lead to cardiac arrhythmia. A study on 138 COVID-19 patients in China revealed that 16.7% of patients developed an arrhythmia, the second most severe complication seen among COVID-19 patients [40]. It is also evident that ICU patients had a higher

occurrence of arrhythmia comparing to non-ICU patients. Another study with 187 hospitalized patients stated that 5.9% developed ventricular tachycardia or ventricular fibrillation [41]. The China CDC also reported that some COVID-19 patients showed symptoms like chest tightness, palpitations, etc. as well [40].

5.2.3. Myocardial Injury, Heart Failure, and COVID-19

Elevated cardiac troponin-I (>28pg/L) in the serum is one of the main causes of cardiac injury [17]. Developing acute cardiac injury is very common amongst the COVID-19 patients as reported in different parts of the world [20]. Increased level of blood creatine kinase (CK), lactate dehydrogenase (LDH), cardiac troponin-I, myocardial dysfunction, or electrocardiographic abnormalities seems to be more common among COVID-19 patients [17, 20, 40, 41]. Elevated levels of troponin and inflammatory biomarkers, myoglobin, serum ferritin, CRP, and IL-6 were found in non-survivors of COVID-19 [17]. A recent study reported that approximately 20% of COVID-19 patients developed a cardiac injury, 10.6% had coronary heart disease, 5.3% had cardiovascular disease and 4.1% had heart failure [20]. A study in China among 191 patients from two hospitals revealed that 23% of corona survivors experienced heart failure and among the non-survivors, 52% had developed heart failure [40, 41]. In addition, several studies across the world showed similar consequences of COVID-19 patients developing a myocardial injury.

5.2.4. Myocarditis and COVID-19

Myocarditis is a well-recognized complication among patients with COVID-19 and it is one of the probable causes of acute cardiac injury. Myocarditis appeared in patients after a prolonged period (approximately 10-15 days) of the infection. Clinically COVID-19 myocarditis may lead to palpitations or mild chest discomfort, which is difficult to distinguish from other causes. Transient change in the ECG report, MRI report, and endomyocardial biopsy can detect myocarditis [40]. A 37 years old man with COVID-19 in China was admitted to the hospital with chest pain, diarrhea, and dyspnea and indicating myocarditis with acute elevation of cTnT and NT-proBNP. Coronavirus particles were found within cytopathic interstitial cells of the myocardium as well in the endomyocardial biopsy of a 69 years old woman with COVID-19 [41].

5.2.5. Thrombosis and COVID-19

COVID-19 hospitalized patients also showed altered coagulation parameters with remarkable elevation in D-dimer and fibrin degradation products in blood. In a cohort study, researchers found an elevated level of D-dimer and fibrin degradation products in non-survivors compared to the survivors. These differences became more apparent during daily measurements and by later stages, 71.4% of non-survivors showed disseminated intravascular coagulation [40, 41].

However, the actual mechanism of SARS-CoV-2 affecting the cardiac system is still unknown. Nevertheless, the

presence of the ACE2 receptor as one of the key components of the renin-angiotensin system and elevated level of IL-6 may illustrate how COVID-19 affecting the cardiac system and thus leading to cardiovascular disease.

5.3. Renal Injury

Studies suggested that COVID-19 patients may develop acute kidney injury (AKI). In a report of 193 cases in China, 60% of cases had proteinuria, 48% cases had hematuria, and 20% showed elevated uric acid (UA), 31% had a higher blood urea nitrogen (BUN) and 22% had a higher serum creatinine levels [43]. Interestingly, the prevalence of AKI has also been observed in the past coronavirus infections, SARS, and MERS [44]. Although the exact etiology of AKI progression is still uncertain, it is expected to be multifactorial related to both the direct and indirect impacts of the infection on the kidney [45, 46]. The ACE2 receptor is abundantly expressed in proximal tubules as well as in podocytes, parietal epithelial cells, collecting ducts, and distal tubules of the kidney [12, 47]. These segments may act as a potential route of entry for the SARS-CoV2 in kidney cells [12]. Besides, SARS-CoV2 presence in the urine of an infected individual also implies the possible renal tropism of the virus [48]. Besides, studies on histopathological analysis of kidneys demonstrate collapsing glomerulopathy, swelling of mitochondria and lysosome, vacuolar degeneration, acute tubular injury (ATI) with loss of luminal brush border, and thrombosis. Furthermore, coronavirus-like particles have been sorted in the renal proximal tubular epithelium as well as in podocytes, and expression of viral nucleoprotein (NP) antigen has been observed in the kidneys [49–53]. Interestingly, similar findings were found in previous coronavirus infections SARS and MERS [54, 55]. Therefore, this evidence suggests the potential direct cytopathic impact of the virus which might lead to the progression of AKI [53].

Additionally, viral-induced cytokine storm may contribute to kidney impairment [56]. Proinflammatory cell infiltration (e.g., CD68+ macrophages, CD56+ natural killer (NK) cells, CD4+ T cells, and CD8+ T cells) have been identified in tubulointerstitium of infected tissue and hyperactivation of these cells may gradually induce epithelial cell apoptosis, fibrosis, and trigger microvasculature alteration. Furthermore, complement-mediated C5-B9 complex or membrane attack complex deposition in tubules has been observed and activation of these complexes triggers renal parenchymal cells to release pro-inflammatory cytokines, profibrotic factors, and ROS that leads to renal injury [53, 57].

The underlying acute respiratory failure (ARDS) syndrome is considered a risk factor for the development of AKI in seriously ill patients [51]. Interorgan cross-talk between lung and kidney may worsen renal performance through several potential mechanisms including hemodynamic instability, biotrauma, hypoxia [58, 59]. Increased levels of proinflammatory cytokines (e.g., IL-6, plasminogen activator inhibitor-1 (PAI-1), soluble TNF-I, and TNF-II receptors) released from injured lungs might contribute to the incidence of AKI in patients with ARDS [58]. Other plausible factors

include ischemia, drug-induced nephrotoxicity, rhabdomyolysis may also contribute to damage to the kidney [49, 60, 61]. AKI amplifies the risk of mortality rate in COVID-19 patients, and hence proper surveillance of renal involvement and effective intervention may help to reduce the fatality [62].

5.4. Neurological Manifestation

Multiple contextual analyses indicate that SARS-CoV-2 has the ability to develop neurological symptoms [13, 22, 63–65]. Techniques like electron microscopy, immunohistochemistry, and real-time reverse transcription PCR have been used to detect the presence of the virus in the brain [63]. A case study of COVID-19 patients in Wuhan showed that about 36.4% of patients (78 out of 214) had experienced various neurological manifestations [66]. SARS-CoV-2 has the potentiality of invading the CNS, like the other members of the coronavirus family [67]. Additionally, neurological injury at some stage in the course of SARS-CoV-2 infection may be related to coagulopathy, with a higher rate of systemic and neighborhood thrombotic events [13]. Three possible pathways have been postulated till now from numerous researches that are used by SARS-CoV to invade the nervous system.

5.4.1. Hematogenous Route

After infecting the respiratory airways, HCoV could cross the basolateral surfaces of epithelial cells into the blood circulation, in a process called viremia [68]. The virus may invade CNS by infecting endothelial cells of the Blood-Brain Barrier (BBB), epithelial cells of the Blood-CSF Barrier, or by using inflammatory cells as Trojan Horse [69]. SARS-CoV-2 may attach to the ACE2 receptor expressed by endothelial cells of the BBB [70]. Once the virus enters into vascular and neuronal tissue, it could begin the cycle of viral budding contacting ACE2 on neurons, glia, and vessels [18]. Circulating with bloodstream SARS-CoV-2 can also infect epithelial cells of the Blood-CSF barrier in the choroid plexus (CP), which is located in the ventricles of the brain [71]. Interestingly, several strains of coronavirus, including SARS, have shown the potentiality to infect numerous types of leukocytes both in vitro and in vivo, where leukocytes serve as a reservoir and vector for neuro-invasive HCoV [69, 72–74]. This mechanism is termed “the Trojan Horse” mechanism, where the affected immune cells move from the blood and get through the BBB to infect the CNS. SARS virus can infect several immune cells, particularly the monocytes, macrophages, and T lymphocytes [72].

5.4.2. Neuronal Retrograde Route

The HCoV virus infects peripheral neurons, like olfactory receptor neurons, the particular trigeminal nerve that lies in the nasal cavity or sensory fibers of the vagus nerve in the brain stem, to invade the CNS by the axonal retrograde transport [69, 75, 76]. Evidence indicated that the virus attacks the CNS by synapses just after invading the peripheral nerve terminals [71]. Loss of sense of smell and

loss of sense of taste illustrate the direct entry of SARS-CoV-2 to the brain via the cribriform plate. SARS-CoV-2 may enter the CNS directly by the olfactory nerve which is likely another possible mechanism for the invasion [18, 70, 71].

5.4.3. Lymphatic Pathway

Several members of the coronavirus family including SARS-CoV, can infect cells involved in intrinsic immunity and thus invade CNS. Besides, SARS-CoV can infect monocyte-derived dendritic cells (DCs). Infected DCs thus transport the virus to the lymphatic tissue, which can be a crucial route of infection [77].

Moreover, studies suggested that COVID-19 patients develop Acute Necrotizing Encephalopathy (ANE), which is associated with cytokine storm. Evidence also indicates that an elevated level of the plasma concentration of different cytokines in the initial stage of COVID-19 infection may also help the virus to invade the CNS [3, 78]. However, further research is needed to comprehend the invading mechanism of COVID-19 to the CNS for better therapeutic development.

5.5. Liver Injury

Several studies suggested that patients with SARS and MERS had developed liver injury during the infection [79, 80]. Generally, coronavirus attacks the pulmonary system and creates problems such as mild respiratory disease to pneumonia but may lead to acute respiratory distress syndrome or multi-organ dysfunction in severe cases [81]. Though some reports support the fact that COVID-19 may cause liver dysfunction but the severity and mortality of this action are still unknown [82–84]. Besides, it is not yet clear whether the liver damage is done directly by viral inclusion or by inflammation response of the immune system [85].

In China, COVID-19 patients had experienced leukopenia, lymphocytopenia, and a higher level of CRP along with acute respiratory failure and severe hypoxemia. In most of these cases, patients were found with septic shock and multiple organ dysfunction. Interestingly, some liver autopsy showed hepatomegaly with dark red, hepatocyte degeneration accompanied by lobular focal necrosis and neutrophil infiltration, infiltration of lymphocytes, and monocytes in the portal area, and congestion of hepatic sinuses with microthrombosis [80].

From the analysis of single-cell sequencing and immunohistochemistry, it is evident that a high level of ACE2 was expressed in the biliary epithelial cells and a very low amount was measured in the hepatocytes [21, 80]. Interestingly, a higher level of ACE2 expression is measured in cholangiocytes rather than in endothelial cells, hepatocytes, and kupffer cells where the expression was minimum [80, 83]. So, it can be predicted that the virus may get into the liver through the bile duct. But it is still unknown whether and how the virus is directly involved in the liver.

According to some studies, a high amount of liver markers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and bilirubin are common in critical patients rather

than in mid-COVID-19 patients. In most of the cases, an elevated number of cytokines, including IL-6, IL-1 β , TNF- α , and cytokine storm is also observed in the liver [82]. However, patients having pre-existing chronic hepatic diseases were found to have an increased level of key liver markers such as ALT, AST, GGT, and total bilirubin [82, 84, 86]. So, in both cases, patients were diagnosed with an elevated amount of liver markers.

The patients who have liver injuries are at higher risk because of the medicine used in the treatment of COVID-19, possible viral load in hepatic cells, hypoxia, and systematic inflammation. Drugs such as antibiotics, antiviral drugs, pain killers, etc., that are used in treating COVID-19 patients may damage the liver as these drugs can create hepatic toxicity [82].

Both the Innate and Adaptive immune system triggers the inflammatory responses and pulmonary injury to COVID-19 patients. Generally, in COVID-19 patients, CD4⁺ T-cells activate B-cells and induce the production of virus-specific antibodies. The presence of a high level of CD8⁺ in the pulmonary interstitium may help to clear the coronavirus from the affected cells and reduce immune injury [80]. One study suggested that in COVID-19 patients lymphopenia and CRP levels independently damaged the liver where inflammatory cytokine storm played a major role [81].

Evidences suggested that the cytokine storms are associated with the adverse outcomes of COVID-19, thus leads to the continuous activation of lymphocytes and macrophages. These cells eventually then secrete a high level of inflammatory cytokines. Typical lymphocytes during the infection may result in an elevated level of IL-2, IL-6, IL-10, and IFN- γ and that might be the reason for liver dysfunction as well [81].

6. Conclusion

SARS-CoV-2 is mainly a respiratory virus but has the potentiality to infect several organs like the heart, liver, kidney, CNS, etc. The spike protein of SARS-COV-2 can recognize the “Angiotensin-Converting Enzyme 2 (ACE2)” receptor of the host cell, which is expressed in many organs in humans. The world is facing a COVID-19 pandemic, which requires a lot of research regarding the development of potential treatment of COVID-19, apparently a safe vaccine. There are more than 100 vaccine candidates enlisted by WHO which are under trial now. To combat the virus, an accurate mechanism of action, clinical features need to be established. Early prognosis of the multi-organ dysfunction following the onset of the disease could help to treat and manage patients effectively in hospital settings. There is emerging evidence of patients suffering from post-COVID-19 multi-organ dysfunction and are requiring various replacement therapies. Further research should be conducted to explore the distinct pathophysiology of multi-organ dysfunction. Besides, the COVID-19 pandemic has made us realize the importance of co-operating between pharmaceuticals companies, governments, and regulatory

agencies. Planning to survive this kind of pandemic should be organized before the occurrence.

Author's Contribution Statement

MAM conceived the idea and revised the manuscript. FS, KZ, AS, and SF contributed to drafting the manuscript. All authors approved the final version of the manuscript.

Conflict of Interest

All the authors do not have any possible conflicts of interest.

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