MODERN MEDICINE AND PRACTICE
https://inovatus.es/index.php/ejmmp
EUROPEAN JOURNAL OF MODERN MEDICINE AND PRACTICE
Vol. 4 No. 9 (Sep - 2024) EJMMP ISSN: 2795-921X

PATHOPHYSIOLOGY OF COVID-19 ASSOCIATED WITH ACUTE KIDNEY INJURY

Nhrawaan M. Wali
Department medical pharmacognosy, College of pharmacy, University of Thi-Qar, Thi-Qar, 64001, Iraq

Teeba T. Khudair
Department of Pharmaceutical Sciences, College of Pharmacy, University of Thi-Qar, Thi-Qar, 64001, Iraq

Rand Ali Zeyad
Department of Medical physiology, College of Medicine, University of Thi- Qar, 64001, Iraq

Abstract: To this day, the new respiratory infectious disease known as coronavirus disease 2019 (COVID-19) has been responsible for the deaths of over 630,000 individuals and the infection of around 15,000,000 people across the globe. This disease was caused by a new strain of zoonotic coronavirus named severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). It was first discovered in Wuhan, China, in December 2019. Most of the patients who passed away had pre-existing conditions; more than twenty percent of them had chronic kidney disease (CKD). In addition, even though SARS-CoV-2 infection is primarily characterized by diffuse alveolar damage and severe respiratory failure, acute kidney injury (AKI) has developed in a significant proportion of cases. It has been demonstrated that acute kidney injury (AKI) is linked to a more dismal prognosis; hence, we believe that the impact of SARS-CoV-2 on the kidney ought to be explored. The pathogenesis of covid 19, the pathophysiology of covid 19 acute kidney injury (AKI), the mechanisms of renal entry-kidney injury, and the clinical aspects of acute kidney injury (AKI) are the topics that are discussed in this article.

Keywords: Covid-19, renal pathology, acute kidney injury, pathogenesis, IL6.

Introduction

SARS-CoV-2, also known as COVID-19, quickly spread globally in December 2019 and, within three months, reached several countries, showing significant rates of illness and death in people with chronic conditions. By November 2020, around 143,900 patients globally have died from this pandemic. COVID-19 symptoms can range from mild to severe, depending on underlying chronic disorders such as pulmonary or cardiovascular diseases and diabetes, which can lead to excessive inflammatory reactions to COVID-19 [1]. Chronic disorders lead to malfunction of endothelial cells, which regulate blood vessel constriction, resulting in increased inflammation and blood clotting. ARDS is the primary cause of death in COVID-19 patients. However, coagulation activation triggered by severe inflammation, thrombosis, and disseminated intravascular coagulation (DIC) also leads to death due to multiple-organ failure syndrome. Although it has been proven that combined prevention and quarantine procedures have been implemented in practically all provinces of mainland China, the SARS-CoV-2 infection is still spreading. It constitutes a significant threat

to public health. Despite this, the virus remains a serious threat to public health for the time being. Thousands of people with severe illnesses have passed away every single day all over the world because of the pressure of clinical therapy and the absence of antiviral therapies. The virology, clinical and molecular epidemiology, diagnosis, etiology, and prospective therapies for treating this infection are all topics covered in this study.

Overview of the COVID-19 Pandemic

Coronaviruses have been responsible for two epidemics known as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [1]. Both epidemics occurred in the past two decades. An unidentified coronavirus, which was subsequently referred to as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), started to spread in Wuhan, China, in December 2019. After that, it quickly spread worldwide, and on March 11, 2020, the World Health Organization (WHO) declared this outbreak a pandemic [2]. The infectious disease caused by SARS-CoV-2 has been granted the official designation of Coronavirus Disease-2019 (COVID-19) by the World Health Organization [3]. When this article was written, the World Health Organization (WHO) claimed that there were slightly more than 236 million confirmed cases of COVID-19 and 4.8 million deaths attributable to the virus worldwide.

SARS-CoV-2 is a member of the Coronaviruses family and has a 79.6% sequence identity with the previously found SARS-CoV-1 [1, 4]. Research conducted by Stockman et al. during the SARS outbreak in 2002–2003 found that patients treated with steroids did not show substantial improvement but experienced side effects, including diabetes, avascular necrosis, psychosis, and extended viremia [5]. SARS-CoV-2 mainly spreads through droplets, aerosols, and direct contact. It can also be found in stool, urine, and blood [6, 7]. The virus enters the host cell by attaching high amounts of angiotensin-converting enzyme II (ACE2) receptors in the lungs, heart, blood vessels, and intestines. After entering the cytoplasm, SARS-CoV-2 releases its genomic RNA and begins replicating within the host cell [1]. The median incubation time is approximately 5.1 days, and 97.5% of symptomatic infections are expected to show symptoms by 11.5 days [8].

In clinical terms, the symptoms of COVID-19 might range from being asymptomatic to having acute respiratory distress syndrome (ARDS) and having dysfunction in many organs. Coughing, fever, headache, irritation of the throat, exhaustion, and shortness of breath are the clinical manifestations that are most frequently observed. In certain patients, the condition may proceed detrimentally, leading to pneumonia, respiratory failure, and ultimately death [9, 10]. This progression is mainly the outcome of a severe inflammatory response characterized by a very high level of inflammatory cytokines and chemokines. Among the various organs extensively affected by the SARS-CoV-2 infection, the kidney is one of the most significantly affected. Investigations have shown that a significant number of patients who have been diagnosed with COVID-19 pneumonia have been presented with FG with multiple forms of renal injuries. In contrast, other patients who have passed away as a result of COVID-19 disease have shown severe kidney damage [11]. Within the scope of this article, we will examine the clinical signs of kidney injury in COVID-19 individuals, with a particular emphasis on the treatments and vaccines that are currently approved and their impact on renal function.

Pathogenesis of COVID-19

1. Receptor Interactions and Cell Entry

The disease-causing stages of COVID-19 are not fully known. The typical belief is that the infection progresses through the following stages [12]. Viral invasion, replication, immune response dysregulation, multi-organ damage, and recovery. The virus enters host cells, replicates, assembles, and is released to target cells, leading to direct injury and destruction of parenchymal cells such as alveolar epithelial cells. Simultaneously, a significant amount of pathogen-associated molecular pattern (PAMP) and damage-

associated molecular pattern (DAMP) molecules are released to trigger the innate immune response, promote inflammatory cell infiltration, release abundant cytokines, chemokines, proteases, and free radicals, leading to acute respiratory distress syndrome (ARDS), sepsis, and multiple organ dysfunction syndrome (MODS). Data suggests that an aberrant immune response plays a more significant role in the consequences of COVID-19 than a direct viral cytopathic effect. Patients with COVID-19 exhibited the highest viral load in the initial stage. The initial stage of viral infection involves receptor recognition and entry, which is crucial in determining tissue tropism. It has been hypothesized that an increased binding affinity between SARS CoV 2 and ACE2 is associated with an increased severity of sickness in humans and an increased likelihood of virus transmission [12]. In a manner analogous to that of SARS-CoV, the human angiotensin-converting enzyme 2 (ACE2) is a functioning receptor that is subverted by SARS-CoV-2 for cell entrance. An enzyme known as ACE2 is a type I membrane protein that is primarily related to cardiovascular illnesses. It is expressed in the colon, kidneys, heart, and lungs. An N-terminal peptidase domain (PD) and a C-terminal Collectrin-like region (CLD) are the components that make up the full-length ACE2 protein. The C-terminal CLD domain concludes with a single transmembrane helix and an approximately 40-residue intracellular region[13]. In addition to cleaving angiotensin (Ang) I, which results in the production of Ang-(1-9) and provides a direct binding site for the S proteins of CoVs, ACE2 is also responsible for this[14]. The S protein of CoVs is found in a metastable pre-fusion conformation, characterized by a significant structural rearrangement that occurs during the process of fusing the viral membrane with the host cell's membrane. This process is initiated by the S1 subunit and a host-cell receptor binding, which causes the pre-fusion trimer to become unstable. Consequently, the S1 subunit sheds, and the S2 subunit transitions to a post-fusion conformation that is highly stable [15].

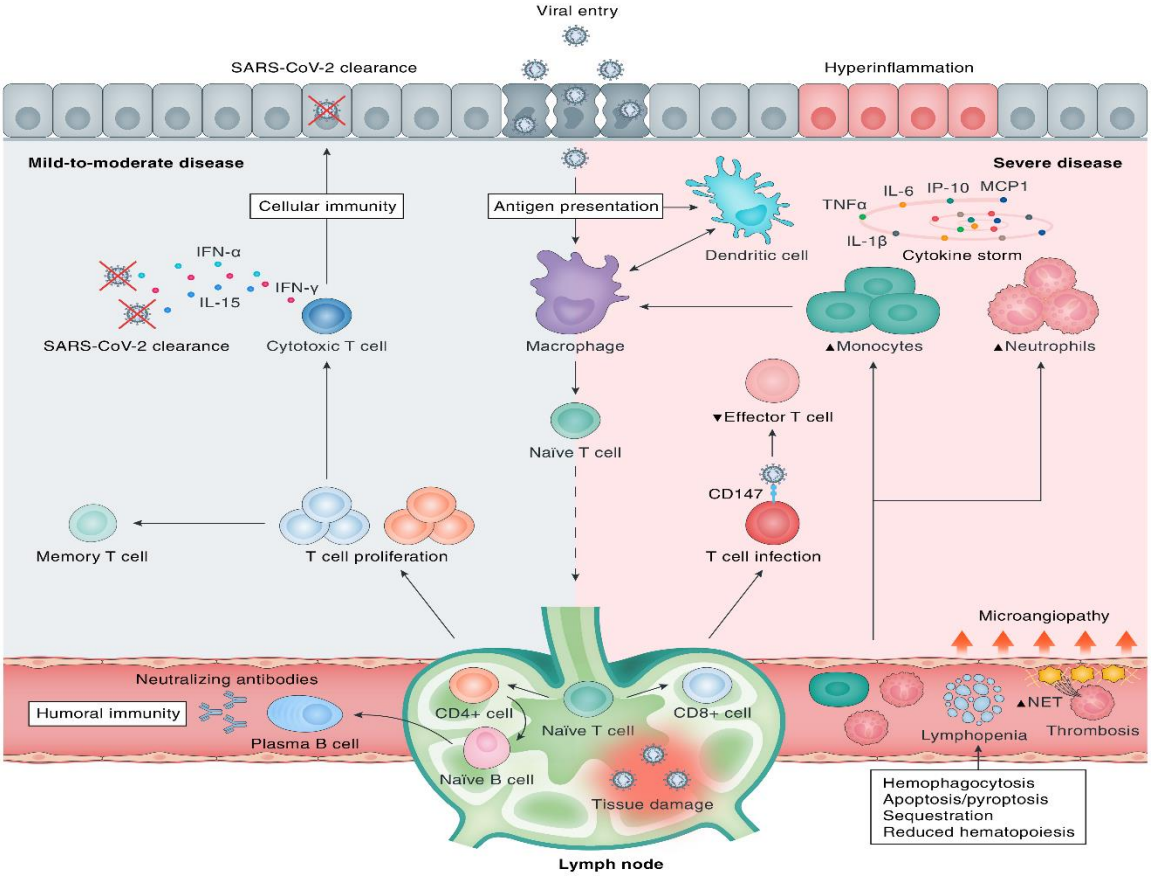


Figure 2. Immunological response to SARS-CoV-2 infection [16]

2**. Direct cytopathic effect of SARS-CoV-2**

Once within the host cells, the virus can reproduce and persist within the specific target cells. The life cycle of SARS CoV 2 is comparable to other single-positive strand RNA coronaviruses. Following replication, new virus particles are generated in the endoplasmic reticulum and discharged from the cell. Simultaneously, target cells either undergo lysis or form syncytia, leading to further lesions. SARS CoV 2 can cause significant damage to host cells, so starting antiviral treatment early may lower the chances of the disease getting worse and leading to death. It is uncertain if SARS CoV 2 affects target cells through several mechanisms to induce host cell damage or apoptosis, such as mitochondrial damage, endoplasmic reticulum stress, intracellular environmental changes (such as pH variations), or enzyme malfunction.

3. Cytokine Release Syndrome

Patients with COVID-19 may experience a life-threatening inflammatory condition called CRS due to the host immune system. This syndrome is characterized by an intense inflammatory response when inflammatory cytokines are quickly released in large quantities in response to infectious stimuli. An uncontrolled inflammatory cytokine storm is a severe condition seen in patients needing admission to the intensive care unit (ICU). The precise mechanisms causing the unchecked production of inflammatory factors have yet to be fully understood. However, there are various proposed ideas. The first is associated with virus replication, resulting in pyroptosis, a very inflammatory type of lytic-programmed cell death (apoptosis). Pyroptosis in COVID-19 patients leads to the release of pro-inflammatory cytokines, impacting the functioning of macrophages and lymphocytes [17], which results in peripheral lymphopenia. The second hypothesis pertains to adaptive immunity and the generation of neutralizing antibodies targeting the virus's surface antigen.

4. Initiation of the innate immune response

One of the most important defense mechanisms against viral infection is the innate immune response, which employs a wide variety of pattern recognition receptors (PRRs) to identify and react to viruses. A close relationship exists between the kind of invading virus, the viral load, the age of the host, and the immune status of the host[18]. The severity of the immune and inflammatory responses of the host is directly related to these factors. In most cases, the innate immune cells of the host are prompted to create cytokines and chemokines that are both antiviral and proinflammatory to destroy the viruses that are infecting the host. A modification in innate immunity that is produced by interferon (INF)-1 is being supported by an increasing body of research. One of the most critical factors in viral replication and the development of adaptive immune systems is interferon-alpha (IFN-1). COVID-19 can influence the host's innate immune response and significantly reduce the function of INF-1 in response to infection. The immunological response is initiated by macrophages, dendritic cells, and neutrophils in the body after a virus infection. These cells serve as the body's first line of defense. In addition, current research indicates that an increased production of certain cytokines, such as IL-6, may be the primary source of the inflammatory response in COVID-19 [19].

5 Cellular immune response

It has yet to be apparent what part T cells, and their subsets play in resistance to COVID 19. Previous research has demonstrated that the S protein belonging to the SARS-CoV virus is the major antigen protein that is responsible for inducing the immunological response of the host. According to Xu et al., it plays a significant part in the activation of cytotoxic T-cell responses and the initiation of humoral immune responses. T helper cells, or T cells, are essential in the adaptive immune system for viral infections. Within the parameters of this scenario, the synthesis of type 1 interferon is insufficient, and the antiviral response is hindered. Th1 cells are indeed primarily capable of regulating the adaptive immune system [20] through the generation of cytokines.

In contrast, cytotoxic T-lymphocytes, also known as CD8+ T cells, can serve as specific mediators to eliminate virus-infected cells. A growing body of evidence indicates that COVID-19 infection affects T lymphocytes, resulting in a reduction in the quantity of CD4+ and CD8+ T cells as well as the levels of interferon-gamma (IFN-γ). Under these circumstances, Th2 responses are heightened, and they are accompanied by an increase in the expression of cytokines that are derived from Th2 cells, such as IL-4, IL-5, and IL-13. Furthermore, a higher proportion of highly proinflammatory T helper 17 (Th17) cells has been observed. Thus, investigating the imbalance in the Th1/Th2 and Th17/regulatory T cell ratios in COVID-19 is a topic that warrants additional research. The decrease in T lymphocytes is directly proportional to the seriousness of COVID-19 in affected individuals. Lymphocytopenia, a deficiency in acquired immunity, is a prevalent characteristic in COVID-19 patients and is associated with increased disease severity and mortality [21]. y. The cause of significant lymphopenia in individuals with severe COVID-19 is still unknown. The cause of lymphopenia is believed to involve hemopoietic tissue depression and direct penetration by virus particles, leading to lymphocyte damage and killing. An effective immune response against viral infections depends on activating cytotoxic T cells to eliminate virus-infected cells. Therefore, enhancing the quantity and activity of T cells is essential for the successful recovery of affected patients.

6 The role of IL-6 signaling in inflammatory status

IL-6 is a glycoprotein exhibiting dual functionality as pro-inflammatory and anti-inflammatory cytokines. It can be generated by stromal cells, nearly all immune cells, and other cell types, including endothelial cells, fibroblasts, keratinocytes, and tumor cells. IL-6 has a vital function in the differentiation of B-cells and the generation of antibodies. IL-6 has other immunomodulatory functions that promote self-reactive pro-inflammatory CD4+ T-cell response, enhance cytotoxic T-lymphocyte activity, and regulate the balance between T-helper 17 and regulatory T-cells. IL-6 can transmit signals through both cis- and trans-signalling routes with different cellular distributions [22]. The first step in the process of intracellular signalling is the binding of IL-6 to its receptor, which is referred to as IL-6R. Subsequently, the IL-6/sIL-6R complex forms an association with the signal-transducing membrane protein gp130. Te gp130 is expressed by most cells in the body, whereas the expression of IL-6R is primarily restricted to immune cells such as neutrophils, hepatocytes, monocytes-macrophages, and some lymphocytes. Currently of molecular-based analysis, the cis-activating pathway is where IL-6 forms a complex by binding to the membrane-bound IL-6 receptor (mbIL-6R), expressed in immune cells. This particular signaling pathway has the potential to predominate at a lower level of IL-6, which is what ultimately mediates the anti-inflammatory effects. In other words, upon attaching IL-6 to its receptor, the complex interacts with gp130, resulting in dimerization and activation of the Janus kinase/ signal transducer and activator of transcription (JAK/ STAT) pathway. There is a substantial correlation between a greater level of IL-6 and severe immune system hyperactivity. This is because gp130 is widely expressed in a variety of effector cells. Taking this into consideration, cis-activation of IL-6 results in several effects on immune systems, including both acquired (B and T cells) and innate (macrophages, neutrophils, and natural killer cells) systems, ultimately leading to the development of CRS conditions. A systemic CRS is the result of JAK/STAT3 activation, which also causes the release of several other cytokines, including IL-8, IL-6, vascular endothelial growth factor (VEGF), MCP-1, and E-cadherin. Pathophysiological abnormalities and lung dysfunction or failure can be caused by vascular endothelial growth factor (VEGF) and E-cadherin, increasing vascular endothelial cell permeability and leaking [23]. On the other hand, the soluble form of the receptor, also known as sIL6R, is present in synovial fluids and serum, and it is responsible for mediating the intracellular signaling cascade. IL-6 stimulates many different types of cells because of this. A disintegrant and metalloprotease 17 (ADAM17) is responsible for the cleavage of mbIL-6R, which results in the formation of the soluble form of Il-6R Classical (cis) signaling is protective and regulates many metabolic processes when the body is in good condition. The IL-6 trans-signaling pathway is

favorably associated with inflammation caused by illness. The IL-6 trans-signaling pathway mediates the differentiation of monocytes into macrophages, recruitment of immune cells, and inhibition of Treg cell function. Recent research suggests that inflammatory cytokines may have a role in developing severe COVID-19. Due to IL-6's crucial function in promoting inflammation, there is a need to create an effective method to block IL-6 signaling, as recommended by worldwide recommendations. Thus, administering neutralizing antibodies to counteract IL-6-induced inflammatory reactions could be a life-saving approach for individuals with COVID-19. Many studies have been conducted to reduce IL-6-induced inflammation, primarily in the later stages of the disease.

7. Hypercytokinemia and organ damage

COVID-19 can result in both pulmonary and systemic inflammation, which can lead to multiple organ dysfunction syndrome (MODS) in high-risk patients. Organ dysfunction is the primary diagnostic criterion for severe or critical cases of SARS-CoV-2 pneumonia. The primary organ dysfunctions in harsh and essential COVID-19 patients include acute respiratory distress syndrome (ARDS), shock, acute myocardial injury, liver injury, kidney injury, and multiple organ dysfunction syndrome (MODS) [15]. Hyper-cytokinemia is an uncontrolled inflammatory condition in the host marked by severe multiple organ dysfunction and increased proinflammatory cytokine reactions. Hyper-cytokinemia has a crucial role in the development of severe inflammation in both severe SARS and COVID-19. COVID-19 can induce a cytokine storm in lung tissues by overstimulating the immune system and causing the unregulated release of cytokines. The term "cytokine storm" describes a range of events that can lead to multiple organ failure and death. Cytokine storms can lead to a severe medical condition called acute respiratory distress syndrome (ARDS). It is not the viral load that causes acute respiratory distress syndrome (ARDS) but rather an overactive immune response. COVID-19 may cause damage to cardiac cells either directly by interacting with the receptors for angiotensin-converting enzyme-2 (ACE2) or indirectly via other mechanisms. Both scenarios are possible. In the case of ACE2 receptors, it is thought that the COVID-19 virus initially assaults several organs that express ACE2 receptors. These organs include the heart, the brain, the arteries, the liver, the kidneys, and the lung, which is the most critical organ. COVID-19 can cause brain harm through both direct and indirect pathways, according to many lines of evidence. Under these circumstances, the development of a hypercoagulable state results in the blockage of cerebral arteries and the subsequent damage to the brain. Additionally, cytokines have the potential to have neurotoxic effects on the brain. They can cause disruptions to the integrity of the blood–brain barrier (BBB), leading to neurological symptoms. The clinical manifestations of these effects are more prevalent in those who have severe types of COVID-19 disease. The cytokine storm caused by COVID-19 also affects the liver, which is another organ. In patients diagnosed with COVID-19, it has been observed that the serum aminotransferase levels were abnormal in between 14.8% and 53.1% of the cases. The activation of the innate and adaptive immune systems, as well as inflammation brought on by virus infiltration and cytotoxic effects, are all factors that contribute to the occurrence of acute kidney injury in COVID-19 patients who have been hospitalized in the intensive care unit[24]. ARDS appears to be the most severe consequence of COVID-19, associated with a significant fatality rate. ARDS is a result of CRS and causes damage to the respiratory epithelium. The pathogenic T cells in these patients generate elevated quantities of cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF), leading to an inflammatory storm and severe lung injury. Based on this notion and findings from a meta-analysis of 38 trials, including 3062 COVID-19 patients, ARDS cases were 19.5%, and the mortality rate was 5.5%. Cytokines play a crucial part in many complications of COVID-19, with IL-6 being able to cause skin lesions. The unregulated release of cytokines can harm multiple organs in COVID-19 patients.

Pathophysiology of Kidney Damage Induced by SARS-CoV-2

Not only has it been demonstrated that ACE-2 is expressed in the lung, but it has also been demonstrated in the liver, stomach, ileum, colon, esophagus, and kidney. These observations, in conjunction with the information that acute kidney injury (AKI) (7%), cardiac dysfunction with abrupt cardiovascular events (12%), and gastrointestinal issues are among the most common clinical signs of COVID-19[23], imply that SARS-CoV-2 is capable of infecting these organs. On the other hand, it is not yet known whether or whether replication of SARS-CoV-2 takes place in these organs, which would result in functional impairment and contribute to the virus's systemic dissemination. According to the findings of several studies, the co-expression of the ACE-2 receptor and TMPRSS genes in kidney epithelial cells was just as significant as in the lung, esophagus, small intestine, and colon [25]. This finding suggests that the kidney may also be a major target organ for SARS-CoV-2. Specifically, podocytes and proximal rectangular tubular cells were shown to have a significant level of co-expression of the ACE-2 and TMPRSS genes [26]. The observations indicate that the virus may lead to AKI by directly damaging kidney cells. The virus could enter the kidney by first invading the podocytes, allowing it to reach the tubular fluid and, subsequently, the proximal tubule cells, where it may attach to ACE-2. Viral replication in podocytes may cause proteinuria and hematuria in many COVID-19 patients. The exact cause of renal dysfunction due to SARS-CoV-2, whether the virus directly causes it or is a result of other systemic processes driven by the virus, has not been clearly determined. Although host immune cells infiltrate infected tissue to control viral replication, their hyperactivation can result in fibrosis, epithelial cell death, and microvasculature damage. Research conducted on SARS-CoV indicated that AKI in SARS patients was caused by particular pathogenic circumstances, namely the cytokine release syndrome [27], as opposed to the kidney being the site of active viral replication, Lymphopenia was observed in patients infected with SARS-CoV-2, according to studies. This was mainly attributed to a significant decrease in the total number of T cells, particularly cytotoxic T lymphocytes (CD8+), as well as an increase in the number of neutrophils and the levels of proinflammatory chemical substances. It was noted that there were significant levels of interleukin-2, interleukin-6, interleukin-10, and interferon-gamma (IFN-γ). In light of this, it has been hypothesized that an increase in inflammatory responses could be the consequence of a loss of T cells that occurs during the viral infection. It is common knowledge that T cells play a significant role in regulating the hyperactive responses of the innate immune system during viral infections. Another considerable discovery concerning COVID-19 is that patients with more severe clinical symptoms have greater serum concentrations of IL-6 and lower IFN-γ levels than those with milder forms [28]. This has occurred primarily because of reduced CD4+, CD8+, and NK cells. The family of cytokines known as interferons (IFN) is essential to the innate immune system's defence against viruses and other microorganisms that cause disease. The interaction between IFN and its receptors triggers a chain reaction of signals, ultimately activating genes that code for proteins that possess antiviral, antiproliferative, or immunomodulatory capabilities. In a typical scenario, the interaction between interferon-gamma (IFN-γ) signals and interleukin-6/sIL-6 receptors (IL-6/sIL-6R) plays a role in the recruitment and subsequent clearance of neutrophils. This interaction plays a significant role in the regulation of infection and the resolution of acute inflammation, as well as in the transition between innate immunity and adaptive immunity [29]. There is a possibility that an increased cytokine storm is associated with a higher IL-6/IFN-γ ratio in individuals who have been infected with SARS-CoV-2. In patients who have COVID-19, these observations indicate that acute kidney injury (AKI) may have an inflammatory origin mediated by a cytokine storm. There is a connection between the cytokine storm and an inflammatory process that begins at a local location and proceeds to spread throughout the body through systemic circulation. Inflammation can lead to organ dysfunction, especially when tissue swelling results in higher pressures outside blood vessels, reducing tissue blood flow. Compensatory repair mechanisms initiate shortly after the onset of inflammation and often can fully restore tissue and organ functionality. Severe inflammation can lead to

fibrosis, resulting in permanent organ damage. During a cytokine storm, the immune system can cause significant harm to organs and normal cells rather than effectively eliminating SARS-CoV-2. [30] A cohort study provided evidence supporting the theory that acute kidney injury (AKI) in COVID-19 patients may result from inflammatory damage, as seen by lower density on kidney CT scans, suggesting inflammation and edema. Severe lung infections may necessitate extended ventilatory assistance and are commonly linked to the cytokine storm. This increases the likelihood of sepsis, characterized by very low blood pressure that need treatment with inotropic medications[31]. In patients with COVID-19 or acute respiratory distress syndrome (ARDS), chronic low blood pressure and narrowing of blood vessels caused by inotropics may contribute to a decrease in kidney filtration and subsequent acute kidney damage. In rhabdomyolysis the massive release of myoglobin due to muscle damage can cause kidney dysfunction. Myoglobin, in fact, shows its renal toxicity through various mechanisms: renal vasoconstriction related to the hyperactivation of RASS by hypoperfusion and the reduction of nitric oxide levels; intratubular cast formation; direct toxicity on renal tubular cells. may be caused by a direct toxic action of SARS-CoV-2, tissue hypoxia from increased breathing, or drug-related harm. In COVID-19 patients who develop rhabdomyolysis, it is likely involved in the development of acute kidney injury (AKI). Erythrocyte aggregation, probably caused by inflammation (shown by a high erythrocyte sedimentation rate) and low blood pressure, can enhance oxidative stress, inflammation, and complement activation, worsening microvascular damage. Erythrocytes blocking small blood vessel passages have been linked to various damage to the inner lining of blood vessels. In endothelial cells of the kidney, only ACE is typically expressed without any detectable ACE[27]. The renal endothelium is not susceptible to direct infection by SARS-CoV-2. Nevertheless, complete exclusion is impossible as ACE-2 expression might be altered in pathological conditions or due to medication.

It is important to highlight that a recent study has identified a novel path for SARS-CoV-2 to invade host cells. This new route involves an alternate cell receptor known as CD147 (sometimes termed basigin), which is a transmembrane glycoprotein and is expressed in all endothelial cells [32]. The hematological profile of COVID-19 patients revealed a state of hypercoagulability, which was discovered through such an analysis. Within these patients, it was found that they had elevated amounts of reactive protein C, fibrinogen, D-dimer, and ferritin in their plasma, all associated with thrombocytopenia. Recently, clinical and autopsy studies from China and the United States have confirmed the development of disseminated intravascular coagulation because of SARS-CoV-2 infection. These findings also include evidence of microangiopathy in several organs. The activation of macrophages that are connected with COVID-19, the storm of cytokines, and the molecular proteins that are related to the damage might trigger the release of tissue factors as well as the activation of coagulation factors that are predisposed to hypercoagulability [33]. This state of hypercoagulability may, in certain instances, be conducive to the progression of acute tubular necrosis into cortical necrosis and, consequently, the development of irreparable kidney impairment. Low back discomfort and microhematuria, both of which were observed in some individuals who tested positive for COVID-19, may be symptoms of renal infarction, according to these observations. In conclusion, the renal damage that was found in patients with COVID-19 is the result of complex mechanisms that were induced directly and indirectly by SARS-CoV-2 [34]. These mechanisms are predisposed to the development of renal dysfunction because of their presence.

Mechanisms of renal entry and kidney injury

The ACE2 proteins are mostly bound by SARS-CoV-2. These proteins are expressed in the kidneys on the brush border of the apical membrane of proximal tubules, and to a lesser extent, they are also described in podocytes [35]. It is, therefore, possible to postulate that the virus reaches the arteriole and the glomerular capillaries and that it initially infects the endothelial cells found in the glomeruli. Consequently, podocytes become infected, and the virus enters the tubular fluid and binds to its receptors in the proximal tubules.

This brings about acute tubular necrosis protein leakage in Bowman's capsule, collapsing glomerulopathy, and mitochondrial impairment. In the beginning, the virus can enter the kidneys through the bloodstream. As a result, many COVID-19 patients were found to have SARS-CoV-2 RNAemia. Even though viremia in COVID-19 individuals is still a topic of discussion, the virus was discovered in extracellular vesicles, which enabled it to move throughout the body and cause harm to several organs, most notably the kidneys. After reverse transcription, the ability of the SARS-CoV-2 virus to incorporate its RNA into the genomic DNA of the host cells is a cause for concern [36]. This may result in the expression of viral proteins in kidney cells, which is a change that may lead to the development of autoimmune disease. COVID-19 can cause kidney damage through either direct infection or systemic effects. These systemic effects include host immune clearance and immunological tolerance disorders, endothelium-mediated vasculitis, thrombus formation, glucose and lipid metabolism disturbance, and hypoxia. The findings revealed that SARS-CoV-2 binds to ACE2 through the S1 subunit, directly causing damage to intrinsic renal cells. This was indicated by direct renal infection being the starting point. Human tissue single-cell RNA sequencing data and ACE2 labeling demonstrated that the kidneys and bladder are enriched with ACE2, which increases the likelihood of viral invasion in these organs [37]. The initial stage of SARS-CoV-2 infection in humans involves the virus contacting the ACE2 receptor on the cell surface. ACE2 binds to the receptor-binding domain (RBD) of the viral spike protein on the surface of SARS-CoV-2. The spike protein undergoes proteolytic cleavage, enabling fusion with cells. Transmembrane protease serine 2 (TMPRSS2) has been identified as the main protease for this mechanism. The inflammatory infiltration of the renal interstitial is mainly composed of lymphocytes and plasma cells, with a few eosinophils. Activated lymphocytes move to kidney tissues to eliminate infected renal cells and produce inflammatory cytokines, causing local inflammation and tissue damage. Cytotoxic particles, including perforin, granulysin, and proinflammatory cytokines, which are abundant in lymphocytes, have a role in causing kidney damage. An excessive release of cytokines results in a cytokine storm [38]. Through its collaboration with renal resident cells and its promotion of tubular and endothelial dysfunction, the cytokine storm has the potential to play a role in acute kidney injury (AKI) in cases of COVID-19. Among all cytokines, interleukin-6 (IL-6) has been pivotal in stimulating renal endothelial cells to release pro-inflammatory chemokines and cytokines. Additionally, it has been shown to enhance kidney vascular permeability, contributing to the microcirculatory system's malfunction[39]. The generation of thrombosis and the induction of capillary leak syndrome are both potential outcomes of pro-inflammatory cytokines, which can lead to the development of disseminated intravascular coagulation] [. In addition, erythrophagocytosis and anemia are found because cytokines can activate macrophages. When taken together, the disruptions of vascular hemostasis, anemia, and damage generated by cytokines are the factors that ultimately result in kidney failure[36]. There is a possibility that the conditions indicated above, in addition to COVID-19, could lead to excessive production of IL-6, which can bind to IL-6 receptors, so causing the activation of vascular endothelial growth factor and a decrease in the expression of E-cadherin, thereby boosting vascular permeability, shock, and MOD.

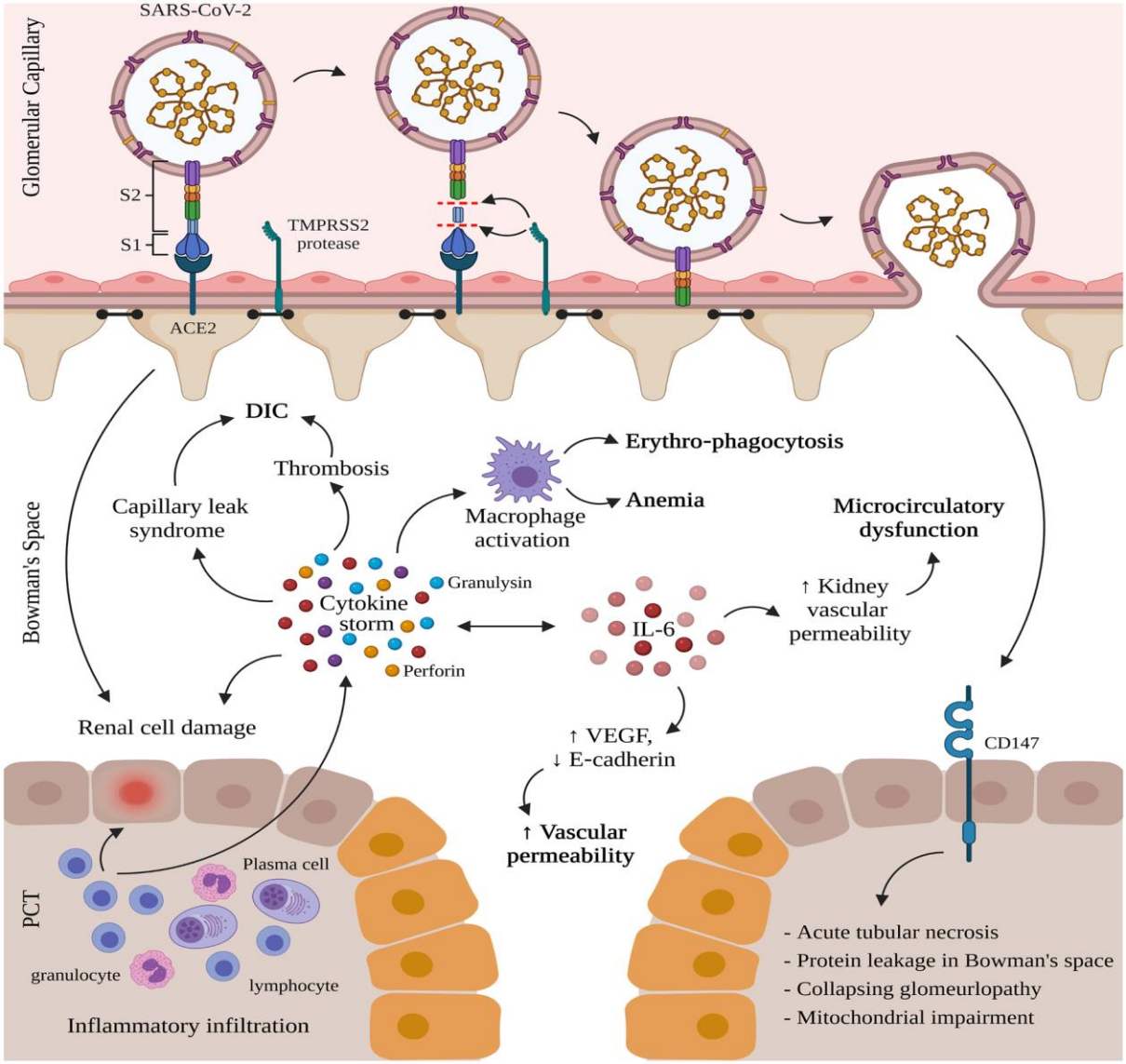


Figure 1; Mechanisms of renal entry and kidney injury in COVID-19 infection [40].

Clinical feature

Early reports of COVID-19 AKI noted the presence of hematuria and/or proteinuria1,18. In one cohort study of 701 patients with COVID-19, 44% and 26% of patients presented with proteinuria and hematuria, respectively 2 ; severity of hematuria or proteinuria (2–3+ on dipstick) was associated with the risk of hospital mortality in a step-wise manner2,18. A more recent cohort study demonstrated much higher rates of proteinuria (defined as a protein-to-creatinine ratio of >0.5, 1+ or higher on dipstick or>30mg/dl on urinalysis) and hematuria (defined as 1+or higher on dipstick or urinalysis), in 80% of patients with COVID-19 AKI 19. Furthermore, >50% of patients without AKI as defined by KDIGO serum creatinine criteria had hematuria and over 70% presented with proteinuria. The presence of urinalysis abnormalities in those not meeting the definition of AKI suggests the existence of kidney injury without notable acute changes in kidney function. Fanconi syndrome (characterized by proteinuria, renal phosphate leak, hyperuricosuria and normo-glycemic glycosuria) has been reported to precede episodes of AKI 25. This presentation is in keeping with stage 1S of new recommendations for AKI staging, when evidence of kidney injury exists that is not detected by creatinine and urine output criteria 26. The proteinuria detected

in patients with COVID-19 AKI is of low molecular weight rather than albuminuria, suggesting a tubular origin rather than glomerular injury, and can be used to identify patients with early-stage AKI27. The contribution of underlying CKD is unknown, but the proportion of patients with COVID-19 and proteinuria far exceeds the prevalence of stage 1 and 2 CKD in the general population 28. Future studies are required to determine the association of biomarkers of glomerular and tubular function with serum creatinine-based AKI in the context of COVID-19 AKI. In addition, these clinical data should be integrated with pathological findings from analyses of kidney biopsy samples 29–33 to gain greater insights into the pathophysiology of COVID-19 AKI. Evidence from a study of biopsy data from 47 patients in France demonstrated that kidney injury seen in cases with the most severe respiratory disease in the ICU is predominantly tubular (66.7%); by contrast, collapsing glomerulopathy and focal segmental glomerulosclerosis were not seen in critically ill patients but were observed in 70.6% of cases not in the ICU[36, 41]. More than two coexisting comorbidities were seen in over 60% of cases and the occurrence of collapsing glomerulopathy correlated highly with the expression of high-risk APOL1 genotypes.

Acute Kidney Injury in COVID-19 Patients

In a 2020 study conducted in China, 75.4% of 333 patients with SARS-CoV-2 infection experienced renal dysfunction characterized by proteinuria and hematuria. The prevalence of Acute Kidney Injury (AKI) was calculated to be 4.7% in the entire group using KDIGO criteria. Patients with severe or critically ill COVID-19 pneumonia showed a higher occurrence of proteinuria and hematuria compared to those with moderate disease. Overall, 43.9% of critically ill patients experienced acute renal injury while in the hospital [42]. Individuals with renal involvement, such as hematuria, proteinuria, and acute kidney injury, had a mortality rate of 11.2%, which was significantly greater than the 1.2% mortality rate observed in individuals without renal involvement. Out of 710 patients brought to Wuhan Jin Yin-tan hospital with proven SARS-CoV-2 pneumonia, 52 were classified as seriously ill. A significant number of patients, including 29% of those with acute kidney injury, required renal replacement treatment [43]. Most patients experienced organ function loss. In addition, blood urea nitrogen (BUN) and serum creatinine levels were elevated in a different study. At the same time, the glomerular filtration rate was low in patients admitted to the hospital with SARS-CoV-2 infection. Among those patients, proteinuria was present in 3.9% and hematuria in 26.7%[44].

Interestingly, individuals who had raised baseline serum creatinine levels exhibited a larger leukocyte count, lower lymphocyte and platelet counts, and anomalies in the coagulation pathway that were linked to a serious condition. It was found that 5.1% of the patients who were hospitalized experienced acute renal injury, with the incidence being highest in the participants who had an elevated serum creatinine level at the beginning of their hospitalization. 33.7% of patients who had elevated baseline serum creatinine, elevated baseline blood urea nitrogen, proteinuria, hematuria, and acute renal damage passed away while they were still in the hospital[39]. According to the findings of another study, acute renal injury occurred in 46 percent of patients who were admitted to the Mount Sinai Health System in the year 2020 with COVID-19. Of those patients, 19 percent required dialysis. The proportions of patients with acute renal injury and those in the intensive care unit differed throughout the five Mount Sinai Health System locations, even though it appeared uniform for all of them. The findings of this study indicate that among the 4,000 individuals with COVID-19 who were admitted to the Mount Sinai Health System, acute renal injury occurred in over half of the patients, and roughly a quarter of those patients required urgent dialysis [44]. An acute kidney injury was found to be independently related to a higher death rate: thirty-five percent of those who survived did not recover kidney function by the time they were discharged from the hospital, and only thirty percent of all patients who suffered an acute renal injury lived and regained kidney function. This current COVID-19 pandemic, similar to the severe acute respiratory syndrome coronavirus outbreak in 2005, has resulted in a higher incidence of acute kidney injury (AKI), opening the door for

prospective future study [36]. This is in comparison to past pandemics that the same virus family has caused. According to a recent Brazilian cohort research, 55% of the patients experienced AKI, with over half of them advancing to stage 3, which was associated with a significantly higher mortality rate compared to patients without AKI. When comparing various populations of COVID-19 patients in different locations and studies, it was found that patients with severe and critical COVID-19 infections were significantly more likely to develop acute kidney injury. This could result in sustained kidney injury, recovery, the need for renal replacement therapy, or death[45]. Common predictor factors for severe acute kidney injury across many trials were advanced age, elevated creatinine and blood urea nitrogen levels upon presentation, male gender, and medical history of hypertension and diabetes.

Overview of Therapy

COVID-19 treatment primarily involves providing support as specific vaccines or medicines are inaccessible. The COVID-19 vaccine is regarded as an effective preventive measure. Approximately 90 universities globally are dedicated to developing a targeted and secure vaccine. By 8 April 2020, there were 115 vaccine candidates in the global research and development landscape for COVID-19[46]. Most of them are in the preclinical phase. However, a few, such as mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologicals, INO-4800 from Inovio, and LV-SMENP-DC and pathogen-specific aAPC from Shenzhen Geno-Immune Medical Institute, have advanced clinical development. The treatment methods commonly utilized for the general population are likewise applied to individuals with chronic renal failure, irrespective of the disease's stage. Antiviral medications such as Lopinavir/ritonavir, Darunavir, Ritonavir, and Darunavir/cobicistat have shown effectiveness in treating SARS-CoV-2 infection in patients with mild symptoms and those with more severe symptoms[41]. In the early phases of the pandemic, the antimalarial medication known as hydroxychloroquine was utilized effectively. However, on May 26, 2020, the Anti-SARS-CoV-2 Food and Drug Administration (AIFA) discontinued authorization to use this medication to treat SARS-CoV-2 infection. In conjunction with steroids and antiviral medications, the anti-IL-6 monoclonal antibody known as tocilizumab has been utilized for the treatment of more severe clinical instances and patients whose levels of D-dimer are fast and considerably growing[47]. The dosage is 8 milligrams per kilogram of body weight, with a maximum infusion dose of 800 milligrams and three administrations. In contrast to hydroxychloroquine, neither antiviral medication nor tocilizumab requires dosage modifications about the values of the glomerular filtrate[48]. Because COVID-19 patients have a high incidence of thromboembolic consequences and a condition of hypercoagulability, the therapy protocols have been modified to include large doses of low molecular-weight heparin. Immunosuppressive medication needs to be redesigned for patients who have received kidney transplants. In particular, mycophenolate, azathioprine, and calcineurin inhibitors need to be discontinued during the active phases of the disease [49]. Tocilizumab, on the other hand, has the potential to be used successfully in these patients; nevertheless, randomized clinical trials are required. The methods that obtain the greatest clearance of the pro-inflammatory molecules are preferred for COVID-19 patients undergoing intermittent dialysis. Continuous dialysis treatments are preferred for patients who have acute kidney injury (AKI), are hemodynamically unstable, and require dialysis [50]. Continuous dialysis treatments include CVVH with pre and post-dilution at a dose greater than 25 mL/Kg/h using citrate as the first choice anticoagulant (after serial assessments of serum calcium and lactic acid) and, alternatively, unfractionated heparin (constantly monitoring the patient's APPT) [51]. The use of interferons has also been suggested as a potential treatment option; however, the timing of their administration is extremely important because the benefits of interferons are only recognized if they are administered before or early on in the infection process [52]. They may even be harmful if they are used later. Clinical trials are now being conducted to evaluate their effectiveness. Recent phosphoproteomics analysis of SARS-CoV-2 infected Vero E6 cells, a cell line derived from monkey kidney epithelial cells, revealed significant alterations in the phosphorylation of both the host and the viral proteins. Additionally, viral infection was found to be responsible for producing

filopodia that contained casein kinase II (CK2) and contained viral particles that were budding. As noted by the authors, pharmacologic inhibition of several kinases, such as CK2 and p38 MAP (mitogen-activated protein) kinases, can potentially be a viable future treatment for COVID-19 [53].

Conclusions

Since COVID-19 is a novel severe respiratory infectious disease, the pathogenic mechanisms of this disease still need to be fully elucidated. This is mostly because this disease is relatively new. Our understanding of the pathogenic processes of COVID-19 is just getting started, even though many important questions still need to be answered at this time. An examination of the pathophysiology of COVID-19 was presented in this review. According to the hypothesis, SARS CoV 2 is responsible for dysregulating the immune inflammatory response in a manner that is comparable to that of SARS CoV and MERS CoV infections. In severe cases of COVID-19, organ failure, hypertyrosinemia, and lymphopenia are the defining characteristics. In individuals with COVID-19, immune dysfunction is a prevalent hallmark. This dysfunction can manifest itself in several ways, including lymphopenia, lower numbers of CD4+ T cells, and aberrant cytokine levels. It can potentially be a significant component related to the severity of the disease and poorer prognosis. Since kidneys play a crucial role in regulating blood pressure and filtering blood from hazardous chemicals, the safety of kidneys in COVID-19 patients continues to be of the utmost importance. For this reason, it is necessary to perform continuous monitoring of the kidneys' function in addition to the hemodynamics of the heart in COVID-19 participants to lessen the impact that COVID-19 has on human life.

Funding

No funding entity for this research.

Conflicts of interest

There are no conflicts of interest.

References

1. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020;382(18):1708-20.
2. Okab HF, Salih MB, Jarulla BA. Immunopathy of COVID-19 Patients without Chronic Disease: Proinflammatory and Anti-Inflammatory Cytokines Attributable to Disease Severity.
3. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney international. 2020; 97(5):829-38.
4. Cheng Y, Luo R, Wang X, Wang K, Zhang N, Zhang M, et al. The incidence, risk factors, and prognosis of acute kidney injury in adult patients with coronavirus disease 2019. Clinical journal of the American Society of Nephrology: CJASN. 2020; 15(10):1394.
5. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney international. 2020; 98(1):209-18.
6. Mohamed MM, Lukitsch I, Torres-Ortiz AE, Walker JB, Varghese V, Hernandez-Arroyo CF, et al. Acute kidney injury associated with coronavirus disease 2019 in urban New Orleans. Kidney360. 2020;1(7):614.
7. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. The lancet. 2020; 395(10239):1763-70.

8. Ng JH, Hirsch JS, Hazzan A, Wanchoo R, Shah HH, Malieckal DA, et al. Outcomes among patients hospitalized with COVID-19 and acute kidney injury. American Journal of Kidney Diseases. 2021; 77(2):204-15. e1.
9. Gupta S, Coca SG, Chan L, Melamed ML, Brenner SK, Hayek SS, et al. AKI treated with renal replacement therapy in critically ill patients with COVID-19. Journal of the American Society of Nephrology: JASN. 2021;32(1):161.
10. Carlson N, Nelveg-Kristensen KE, Freese Ballegaard E, Feldt-Rasmussen B, Hornum M, Kamper AL, et al. Increased vulnerability to Covid-19 in chronic kidney disease. Journal of internal medicine. 2021;290(1):166-78.
11. Fu EL, Janse RJ, de Jong Y, van der Endt VH, Milders J, van der Willik EM, et al. Acute kidney injury and kidney replacement therapy in COVID-19: a systematic review and meta-analysis. Clinical kidney journal. 2020;13(4):550-63.
12. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. nature. 2020;579(7798):270-3.
13. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450-4.
14. Okab HF, Salih MB, Jarulla BA. Evaluation of CXCL 10 and IL-10 in COVID-19 pneumonia. Pneumologia.;71(4):175-80.
15. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. jama. 2020;323(11):1061-9.
16. van Eijk LE, Binkhorst M, Bourgonje AR, Offringa AK, Mulder DJ, Bos EM, et al. COVID-19: immunopathology, pathophysiological mechanisms, and treatment options. The Journal of pathology. 2021;254(4):307-31.
17. Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerging microbes & infections. 2020;9(1):382-5.
18. Cao X. COVID-19: immunopathology and its implications for therapy. Nature reviews immunology. 2020; 20(5):269-70.
19. Arabi YM, Murthy S, Webb S. COVID-19: a novel coronavirus and a novel challenge for critical care. Intensive care medicine. 2020;46:833-6.
20. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The lancet. 2020;395(10224):565-74.
21. Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265-9.
22. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. bmj. 2020;368.
23. Wan Y, Shang J, Sun S, Tai W, Chen J, Geng Q, et al. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. Journal of virology. 2020;94(5):10.1128/jvi. 02015-19.
24. McBride R, Fielding BC. The role of severe acute respiratory syndrome (SARS)-coronavirus accessory proteins in virus pathogenesis. Viruses. 2012;4(11):2902-23.

25. Cao J, Tu W-J, Cheng W, Yu L, Liu Y-K, Hu X, et al. Clinical features and short-term outcomes of 102 patients with coronavirus disease 2019 in Wuhan, China. Clinical Infectious Diseases. 2020;71(15):748-55.
26. Iwasaki A, Pillai PS. Innate immunity to influenza virus infection. Nature Reviews Immunology. 2014;14(5):315-28.
27. van der Poll T, Opal SM. Host–pathogen interactions in sepsis. The Lancet infectious diseases. 2008;8(1):32-43.
28. Liu X, Chen Y, Tang W, Zhang L, Chen W, Yan Z, et al. Single-cell transcriptome analysis of the novel coronavirus (SARS-CoV-2) associated gene ACE2 expression in normal and non-obstructive azoospermia (NOA) human male testes. Science China Life Sciences. 2020;63:1006-15.
29. Chen Q-L, Li J-Q, Xiang Z-D, Lang Y, Guo G-J, Liu Z-H. Localization of cell receptor-related genes of SARS-CoV-2 in the kidney through single-cell transcriptome analysis. Kidney Diseases. 2020;6(4):258-70.
30. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng C-TK. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. Journal of virology. 2009;83(7):3039-48.
31. Lei Z, Cao H, Jie Y, Huang Z, Guo X, Chen J, et al. A cross-sectional comparison of epidemiological and clinical features of patients with coronavirus disease (COVID-19) in Wuhan and outside Wuhan, China. Travel medicine and infectious disease. 2020;35:101664.
32. Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, et al. AKI in hospitalized patients with COVID-19. Journal of the American Society of Nephrology. 2021;32(1):151-60.
33. Yang D, Xiao Y, Chen J, Chen Y, Luo P, Liu Q, et al. COVID-19 and chronic renal disease: clinical characteristics and prognosis. QJM: An International Journal of Medicine. 2020;113(11):799-805.
34. Li G, Ge Y, Sun Z, Luo S, Wang W, Zhou C, et al. Correlation Study of Chest CT Features of Severe/Critical type COVID-19 with Early Renal Damage and Clinical Prognosis. 2020.
35. Wang M, Xiong H, Chen H, Li Q, Ruan XZ. Renal injury by SARS-CoV-2 infection: a systematic review. Kidney Diseases. 2021;7(2):100-10.
36. Hamming I, Timens W, Bulthuis M, Lely A, Navis Gv, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland. 2004; 203(2):631-7.
37. Asehnoune K, Villadangos J, Hotchkiss R. Understanding host–pathogen interaction. Intensive care medicine. 2016; 42:2084-6.
38. Streicher F, Jouvenet N. Stimulation of innate immunity by host and viral RNAs. Trends in Immunology. 2019; 40(12):1134-48.
39. Zhou J, Chu H, Li C, Wong BH-Y, Cheng Z-S, Poon VK-M, et al. Active replication of Middle East respiratory syndrome coronavirus and aberrant induction of inflammatory cytokines and chemokines in human macrophages: implications for pathogenesis. The Journal of infectious diseases. 2014; 209(9):1331-42.

40. Faour WH, Choaib A, Issa E, Choueiry FE, Shbaklo K, Alhajj M, et al. Mechanisms of COVID-19-induced kidney injury and current pharmacotherapies. Inflammation Research. 2022:1-18.
41. To K, Lo AW. Exploring the pathogenesis of severe acute respiratory syndrome (SARS): the tissue distribution of the coronavirus (SARS-CoV) and its putative receptor, angiotensin-converting enzyme 2 (ACE2). The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland. 2004; 203(3):740-3.
42. Chen Y-T, Shao S-C, Hsu C-K, Wu I-W, Hung M-J, Chen Y-C. Incidence of acute kidney injury in COVID-19 infection: a systematic review and meta-analysis. Critical Care. 2020;24:1-4.
43. Zahid U, Ramachandran P, Spitalewitz S, Alasadi L, Chakraborti A, Azhar M, et al. Acute kidney injury in COVID-19 patients: an inner city hospital experience and policy implications. American journal of nephrology. 2020; 51(10):786-96.
44. Sabaghian T, Kharazmi AB, Ansari A, Omidi F, Kazemi SN, Hajikhani B, et al. COVID-19 and acute kidney injury: a systematic review. Frontiers in medicine. 2022; 9:705908.
45. Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. Acute kidney injury in critically ill patients with COVID-19. Intensive care medicine. 2020; 46:1339-48.
46. Stasi C, Fallani S, Voller F, Silvestri C. Treatment for COVID-19: An overview. European journal of pharmacology. 2020; 889:173644.
47. Menéndez JC. Approaches to the potential therapy of COVID-19: a general overview from the medicinal chemistry perspective. Molecules. 2022;27(3):658.
48. Lee C, Choi WJ. Overview of COVID-19 inflammatory pathogenesis from the therapeutic perspective. Archives of pharmacal research. 2021;44(1):99-116.
49. Khalili M, Chegeni M, Javadi S, Farokhnia M, Sharifi H, Karamouzian M. Therapeutic interventions for COVID-19: a living overview of reviews. Therapeutic advances in respiratory disease. 2020; 14:1753466620976021.
50. Das G, Ghosh S, Garg S, Ghosh S, Jana A, Samat R, et al. An overview of key potential therapeutic strategies for combat in the COVID-19 battle. RSC advances. 2020;10(47):28243-66.
51. Kumari M, Lu R-M, Li M-C, Huang J-L, Hsu F-F, Ko S-H, et al. A critical overview of current progress for COVID-19: development of vaccines, antiviral drugs, and therapeutic antibodies. Journal of biomedical science. 2022; 29(1):68.
52. Li G, Hilgenfeld R, and Whitley R, De Clercq E. Therapeutic strategies for COVID-19: progress and lessons learned. Nature Reviews Drug Discovery. 2023;22(6):449-75.
53. Shi Y, Wang G, Cai X-p, Deng J-w, Zheng L, Zhu H-h, et al. An overview of COVID-19. Journal of Zhejiang University Science B. 2020; 21(5):343.