SciencePG
Science Publishing Group

COVID-19: Associated Acute Kidney Injury (AKI) Pathology and Therapies from Complementary and Alternative Medicine

Md. Aminul Islam Apu[1, 2, *], Aar Rafi Mahmud[3], Md. Rifat Sarker[3], Dibyendu Halder[3], Nova Rahman[4], Md. Shahporan Shuvo[3], Raihana Akter Nira[5]

[1]Department of Biotechnology and Genetic Engineering, Islamic University, Kushtia, Bangladesh

[2]ABEx Bio-Research Center, Dhaka, Bangladesh

[3]Department of Biochemistry and Molecular Biology, Mawlana Bhashani Science and Technology University, Tangail, Bangladesh

[4]Department of Biochemistry and Molecular Biology, Jahangirnagar University, Dhaka, Bangladesh

[5]Department of Accounting and Information Systems, Islamic University, Kushtia, Bangladesh

Email address:

aminul.btge@gmail.com (Md. Aminul Islam Apu), aarrafimahmud21@gmail.com (Aar Rafi Mahmud),
rifatsarker922@gmail.com (Md. Rifat Sarker), dibyodikshit@gmail.com (Dibyendu Halder), novarahman10@gmail.com (Nova Rahman),
shuvoshahporan@gmail.com (Md. Shahporan Shuvo), nira.aiuiu@gmail.com (Raihana Akter Nira)
[*]Corresponding author

Abstract: More frequently than first believed, kidney involvement after SARS-CoV-2 infection is linked to morbidity and mortality. Similar to the etiology of other types of AKI, the pathophysiology of COVID-19 AKI is most likely complex. Although rates of COVID-19 AKI vary significantly across studies and geographical areas, the information currently available points to an incidence of > 20% in hospitalized patients. There are several similarities between COVID-19 AKI and AKI resulting from non-viral causes observed in the ICU, including risk factors, potential processes, and prognosis. Despite noticeably decreased kidney function, acute tubular damage is frequently present, even though it is often minor. Tubular damage most likely results from systemic hemodynamic instability. Despite COVID-19 being referred to as a cytokine storm syndrome, patients with COVID-19 frequently have lower amounts of circulating cytokines than those with acute respiratory distress syndrome from causes other than COVID-19. The prevention and treatment of COVID-19 AKI are poorly understood. Regional'surges in COVID-19 cases might restrict hospital resources, particularly the availability of supplies for dialysis; as a result, thorough daily monitoring of the resources at hand is required. Based on the most recent research, the Acute Disease Quality Initiative recommends diagnosing, preventing, and managing COVID-19 AKI in this Consensus Statement. Additionally, we sought to enhance comprehension of the underlying mechanisms and enhance patient outcomes for COVID-19 AKI. It is essential to comprehend the core molecular mechanisms and the pathophysiology of kidney damage and AKI in COVID19 to create appropriate management plans and therapeutic designs.

Keywords: SARS-CoV-2, COVID-19, Kidney Injury, Acute Kidney Injury, Kidney Transplant

1. Introduction

A brand-new coronavirus called the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was found in China in December 2019. The coronavirus disease 2019 (COVID-19), which is brought on by this virus, is characterized by diffuse alveolar destruction that results in an acute respiratory distress syndrome [1]. Although acute

kidney injury (AKI) is now recognized as a prevalent consequence of the disease and is frequently seen at hospital admission, the pulmonary signs of COVID-19 are still the most conspicuous. Initial reports from China claimed kidney involvement rates were relatively low [2-4], but later findings from the USA and Europe show that AKI rates are significantly higher [5-8]. In addition, compared to individuals with normal kidney function, these patients displayed lower platelet and lymphocyte counts, greater leucocyte counts, a higher risk of comorbidities, and a requirement for intensive care. However, mounting evidence suggests that AKI is very common among COVID-19 patients, particularly those in the intensive care unit (ICU) [9]. Although the reported rates of AKI are pretty variable, the information that is now available indicates that it probably affects more than 20% of hospitalized patients and more than 50% of ICU patients [9, 10]. Similar to how AKI is linked to other types of pneumonia acquired in the community [11]. The pathophysiology of renal disease in people with COVID19 may entail a variety of causes [12, 13]. The angiotensin-converting enzyme 2 (ACE2), which serves as a SARS-CoV2 receptor, may be directly involved in the virus's first effects on the renal parenchyma. The genes for ACE2 and transmembrane protease, serine 2 (TMPRSS2) are expressed in kidney cells at levels comparable to those seen in the lung, small intestine, and esophagus, indicating their significance as SARS-CoV2 targets [14].

Furthermore, current research points to podocytes and proximal convoluted tubules expressing the ACE2 gene as significant SARS-CoV2 host cells, suggesting that the renal tissue may be a potential SARS-CoV2 target [15]. Beyond its role as a viral receptor, ACE2 may link the renin-angiotensin system (RAS), the kallikrein-kinin system, and COVID-19 (KKS) [16, 17]. In this review, we first discuss the dispute surrounding SARS-CoV-2 and its direct function in kidney infection. We then define AKI in COVID-19 based on the injury pattern and thoroughly characterize all documented histological abnormalities.

2. COVID-19

A pneumonia outbreak with an underlying etiology was reported in December 2019 in Wuhan, Hubei Province, China. The subgenus Sarbecovirus includes the betacoronavirus SARS-CoV-2. The outbreak has cost the world extensively regarding lost human lives, adverse economic effects, and rising poverty [18]. A polybasic cleavage site at the S1/S2 spike junction regulates infectivity and host range and the virus's optimum affinity for the angiotensin-converting enzyme 2 (ACE2) receptor, which are two traits that distinguish SARS-CoV-2 from other coronaviruses. [18-20]. Although other organ systems are also affected, the SARS-CoV-2 virus principally affects the respiratory system [21, 22]. The earliest case series from Wuhan, China, reported lower respiratory tract infection-related symptoms such as fever, dry cough, and dyspnea. Other symptoms, e.g., such as vomiting, diarrhea, headache,

and widespread weakness, were noted [22, 23]. It is now commonly acknowledged that COVID-19's respiratory symptoms are incredibly diverse, ranging from hardly noticeable symptoms to severe hypoxia with Acute Respiratory Distress Syndrome (ARDS) [22]. Coronaviruses are positive-sense, single-stranded, enclosed RNA viruses about 30 kb in size [24]. Various host species are infected by them [25]. Based on their genetic structure, they are generally split into four genera: α, β, γ, and δ. Only mammals can get infected by α and β coronaviruses [26]. The common cold and croup are caused by human coronaviruses like 229E and NL63, which are in the coronavirus family [22]. Four structural proteins are found within coronaviruses: spike (S), membrane (M), envelop (E), and nucleocapsid (N) [27]. Spike a transmembrane trimetric glycoprotein that protrudes from the virus's surface and controls host tropism and coronavirus diversification [22, 27]. Spike comprises two functional subunits: the S1 subunit binds to the host cell receptor, and the S2 subunit joins the viral and cellular membranes. SARS-CoV functional receptor angiotensin-converting enzyme 2 (ACE2) has been identified [28]. The spike for SARS-CoV-2 also linked to ACE2, according to structural and functional studies [29-31]. ACE2 was highly expressed in ileum, kidney, bladder, lung, and heart [32]. The lower respiratory tract in humans can be affected by coronaviruses. These potential pathogens can cause illnesses ranging from a simple cold to severe infections with up to 50% mortality [33, 34]. COVID-19 presents an acute upper and lower respiratory tract infection that develops into pneumonia and impacts numerous other tissues and organs, including the kidneys [35, 36]. The most common symptoms were fever, coughing, acute exhaustion, viral illnesses, and pneumonia. [1, 36, 37]. Although most patients have a mild form of the disease, some patients can develop respiratory failure, arrhythmias, shock, kidney failure, cardiovascular damage, or liver failure, especially if they suffer from other diseases [36, 38, 39]. According to a current study, fever, cough, and extreme tiredness were present in 81.2%, 58.5%, and 38.5% of cases, respectively [34]. The most prevalent symptom in COVID-19 patients is a fever, though still, not all individuals experience this. Vomiting and fever (over 39 degrees) are typically indicators of more severe sickness and a more extended hospital stay, but fever is a concerning indicator of the illness [21, 36, 40]. Vomiting and fever (over 39 degrees) are typically indicators of more severe sickness and a more extended hospital stay, but fever is a concerning indicator of the illness [34, 36]. Although COVID-19 cannot be detected early on by the immune system, research and clinical evidence indicate that SARS-CoV-2 may be colonized in the nasopharynx. Sneezing and runny nose are two examples of how the body might naturally rid itself of the infection. Patients with COVID-19 exhibit a wide range of impairments and organ dysfunctions. Depending on the patient, the disease's progression varies from asymptomatic infection to severe symptoms and even fatal events [41-43]. Pathological alterations in the kidney during COVID-19-associated AKI include tubulointerstitial, glomerular, and

vascular destruction [43]. A study finds out that the kidney image shows extensive injury in the proximal tubule with brush border loss and severe necrosis, as well as vacuolar degeneration and tubulointerstitial fibrosis [43]. SARS-CoV-2 viruses are visible in the tubular epithelium using electron microscope imaging, especially in the proximal tubule and podocytes [42-44]. Infiltrate is formed by inflammatory cell types, and edema can be noticed in the interstitial compartment [43]. Infiltrating inflammatory cell types and edema can be detected in the interstitial compartment. The basement membrane is the only obstacle between the filtrate and the peritubular interstitium in the severe case of kidney injury. Due to elevated endothelial permeability, glomerular filtrate spills into the interstitium from the tubular lumen [44]. Autopsies from the kidneys of COVID-19 patients have shown diffuse and focal segmental fibrin thrombus in the glomerular capillary loops and endothelial damage [43]. Collapsing glomerulopathy is characterized by loss of podocyte integrity and glomerular epithelial degeneration. Glomerular capillaries become segmentally or universally collapsed and dysfunctional due to hyperplasia and hypertrophy of the glomerular epithelium. [43]. A reduction in GFR and an increase in SCr are indicators of further damage. The baseline functional reserve is constrained by underlying chronic renal disease or aging-related variables, which might accelerate the onset of acute kidney injury (AKI) [45].

3. Acute Kidney Injury

Acute kidney injury is referred to as damage to the kidney tubule cells. Evidence to date shows that acute kidney injury was the primary cause of the great majority of AKI cases in COVID-19 individuals and the main pathological finding in Acute kidney injury [46]. The study of kidney autopsy and kidney Histopathology also indicates that acute kidney injury was observed in the kidneys of individuals who had severe COVID-19 infection and died [47, 48]. From a kidney histopathology survey of 42 individuals who died from COVID-19, One of the most important discoveries was a mild acute kidney injury. Acute kidney injury may occur due to Long-term volume depletion and hemodynamic conditions that lower kidney perfusion. When COVID-19 is severe, immune cells are recruited by the viral infection in type II alveolar cells, which produces an excess of cytokines that might cause circulatory collapse [49]. Kidney injury is also likely caused by systemic hemodynamic instability and increased renal interstitial pressure brought on by tissue edema. The kidney damage caused by SARS-CoV-2 is anticipated to be complex; it can be directly infected by Podocytes and proximal kidney cells [50]. Acute kidney injury and diminished glomerular filtration rate (GFR) are related, this relation between them gives rise to three potential ways that the renal tubular epithelial cells might be damaged: [51]

1) Tubuloglomerular Feedback induces afferent arteriolar vasoconstriction.
2) Glomerular filtrate leakage backward.

3) Blockage in the tubes.

Some symptoms of acute kidney injury due to COVID-19 are splenic infraction or showing signs of hematuria and loin discomfort. Circuit clotting is more often in COVID-19 patients receiving hemodialysis [52]. Treatment of acute kidney injury may include preventing hypovolemia or hypotension; patients with low blood pressure should stop using ACEI or angiotensin II receptor blockers. Additionally, intravenous (IV) fluids such as crystalloids should be used to optimize volume status and maintain appropriate renal blood flow. Medications that can lead to acute kidney injury, such as Nephrotoxic medications (NSAIDs), and antibiotics, such as vancomycin and radiocontrast agent, should be avoided [51]. For the treatment of acute renal damage, Renal Replacement Therapy (RRT) may also be the preferable option. In conclusion, acute kidney injury appears in individuals inevitably in the presence of severe COVID-19, but it is frequently moderate despite severely compromised kidney function [53].

Collapsing glomerulopathy is also associated with acute kidney injury in patients with COVID-19 [54], and It typically goes together with acute kidney injury, kidney dilation with microcyst formation, and interstitial inflammation [55]. Collapsing glomerulopathy (CG) is a severe and distinctive histologic variation of focal segmental glomerulosclerosis defined by segmental or global glomerular cluster breakdown, along with overlaying podocyte enlargement and proliferation [56]. Collapsing glomerulopathy was First discovered in the context of HIV infection and later became known as the typical Histomorphology type of HIV-associated nephropathy (HIVAN) [67].

3.1. COVID-19-Associated AKI Pathophysiology

The lungs are the most known affected organ by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Entry of this virus is regulated by the help of ACE2angiotensin-converting enzyme 2, expressed in the lungs, heart, brain, intestine, liver, pharynx, and other tissue [58]. But among, various organ abnormalities, dysfunctional syndromes, and cardiac and renal functional disturbance are the prevalent symptoms present in patients who die from COVID-19 [69]. AKI (acute kidney injury) is a clinical marker of faster decline in kidney activity due to the effect of various inducers. It is closely associated with health problems and death [60]. The invading viruses may infect the lungs, travel via the bloodstream, and infect the kidneys, where they might build up and harm local cells.

Consequently, the kidney is one of the extrapulmonary organs that is frequently affected [61]. Therefore, COVID-19 is a threat by itself and affects patients suffering from renal abnormalities in a worsened way. A study in New York showed that 454 of the 5700 hospitalized COVID-19 patients had the renal illness. Five hundred fifty-three patients faced death out of the 5700 patients, while 81 were administered renal replacement treatment [62]. Another study showed that 8.3% of patients suffering from AKI and COVID-19 in

Wuhan Zhongnan Hospital were admitted to ICU out of the 138 patients, while only 2% were non-ICU patients [63]. Typically, COVID-19-induced kidney injury shows up as tubular destruction and evident urinalysis abnormalities. In addition, it is usually associated with a rise in creatinine and urea nitrogen level. Abnormal glomerular filtration is also visible in patients [35]. One study conducted among 59 patients (COVID-19 affected) visualized that the creatinine level was higher in 19% of patients, while 27% had elevated urea nitrogen levels [64]. From this, it can be seen that understanding the clinical characteristics of COVID-19 infection with kidney damage is crucial to the prevention and treatment of COVID-19.

Critically sick patients frequently develop acute kidney damage (AKI), linked to significant health problems and mortality. Although COVID-19s primary symptoms are respiratory failure, pulmonary manifestation, or hypoxia, renal abnormalities are frequently seen. Studies have prioritized observing different respiratory complications during the onset of the new SARS-CoV-2 pandemic. Consequently, less attention was given to AKI incidence in those patients [65]. But recently, much research has been conducted on AKI and its relationship with COVID-19. Several reports have now established AKI as a widespread complication of the disease. Studies showed that almost 45% of ICU patients need renal therapy [5, 6] due to AKI. The pathophysiology of COVID-19-associated AKI has not been adequately elucidated yet. However, current findings from studies suggest two mechanisms: specific mechanisms and unspecific mechanisms. A Specific mechanism involves a receptor named ACE2, which is highly expressed in the kidney. Non-specific factors, for example, hypoxia, low cardiac output, hypotension, and hypertension, might contribute to this pathophysiology [66].

3.2. SARS-CoV-2 Invasion in the Kidney

A variant of ACE is called angiotensin conversion enzyme 2 (ACE2). Angiotensin 2 is changed into angiotensins 1 through 7. It reduces renin-angiotensin system activity, which induces vasoconstriction [67]. ACE2 possesses a membrane-bound form associated with SARS-CoV-2 during cellular invasion [66]. Cell invasion also requires the presence of a protease named Transmembrane protease, seine 2 (TMPRSS2), that can break down viral spikes [68]. The RAAS (renin–angiotensin–aldosterone system) and ACE-2 play essential roles in SARS-CoV-2 infection. Renin converts angiotensinogen into angiotensin-1, which then undergoes a second conversion to become angiotensin two by ACE. As a result, the harmful repercussions of Raas activation are caused by angiotensin-2 [67]. ACE-2 counteracts this negative impact. By converting angiotensin-1 into angiotensin (1-9), ACE-2 combats the harmful consequences of RAAS activation. SARS-CoV-2 invades the cellular system by forming a complex with ACE-2, which results in the declination of this membrane-bound conversion enzyme. Insufficient ACE-2 triggers aggregation of angiotensin-II, which causes the RAAS to be imbalanced,

increasing inflammation, fibrosis, and vasoconstriction [66, 69]. According to mounting proof, inflammatory cytokines are raised in severe COVID-19 patients, primarily when referred to the intensive-care unit. In severely ill patients, IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, and TNF-α levels were greater [21]. Via associating with renal native cells and triggering endothelial and tubular malfunction, these peptides may promote AKI in COVID-19 patients. Example: IL-6 concentrations in critically ill COVID-19 individuals have been confirmed excessive in some investigations [70]. Variants of AKI, such as ischemic AKI, nephrotoxin-induced AKI, and sepsis-induced AKI, have demonstrated that IL-6 exerts detrimental impacts [71]. Clinical studies showed that the corona family viruses' ability to cause glomerulopathy was minimal; however, immune complexes deposition of viral particles or virus-induced particular immunological abnormalities are still possible [72]. The expression of the genes for ACE2 and transmembrane protease, serine 2 (TMPRSS2) in kidney cells is comparable to that in the lung, small intestine, and esophagus, suggesting their significance as SARS-CoV2 targets. Beyond its role as a viral receptor, ACE2 may link the renin-angiotensin system (RAS), the kallikrein-kinin system (KKS), and COVID-19. When SARS-CoV-2 binds to ACE2, ACE2 activity is reduced, upsetting the physiological balance between ACE and ACE2, which results in the loss of angiotensin-(1-7protective)'s effects and an accumulation of angiotensin-II. This encourages vasoconstriction, inflammation, and glomerular dysfunction, leading to AKI [72].

The kidney can be directly infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which invades cells and uses the host cell's machinery for replication. SARS-CoV-2 infection of the proximal tubules is likely accompanied by the presence of virions in the urine [73]. Dehydration was one of the potential contributing factors to the renal abnormalities caused by COVID-19; this condition could be brought on by a fever or by an older adult's decreased fluid intake. Dehydration affects the kidney in several ways, reducing the glomerular filtration rate and leading to acute renal damage [72].

3.3. Non-Specific Factors

There is a decent chance that some other parameters besides the virus have a role in the etiology of AKI in the scenario of COVID-19, including drug toxicity, hemodynamic parameters, and the influence of organ infrastructures. Renal hypoperfusion and acute tubular injury may emerge from acute hypoxemia's potential to interfere with renal function and increase renal vascular resistance [75, 76]. Patients having severe COVID-19 have quite an increased chance of AKI after getting automated ventilation [77]. The cardiovascular system and kidneys are most likely to collaborate to promote COVID-19-induced AKI. Myocarditis and myocardial infarction are acute cardiovascular system abnormalities. Patients suffering from myocarditis and myocardial infarction along with COVID-19 may damage cardiac output. In addition, it may impair

kidney oxygenation through a diminution of cardiac production or congestion of the renal venous system [78, 79]. The most obvious cause of severe COVID-19 infection in hospitalized patients is acute respiratory distress syndrome (ARDS) [80]. In addition, severe hypoxemia and inadequate gas exchange have been categorized as risk factors for AKI in ARDS patients [66]. Most COVID-19 patients with AKI are older and typically have coexisting conditions such as high blood pressure or diabetes mellitus [80, 81]. These elements have been recognized as well-known contributors to AKI development in individuals with severe respiratory failure [82]. Moreover, individuals suffering from these conditions are being treated with drugs that hinder normal renal flow. This could be relevant since several patients had a persisting fever, trouble breathing, and digestive issues, leading to subsequent pre-renal AKI [21, 81].

4. Factors Causing Acute Renal Damage Linked to COVID-19

One well-known side effect of coronavirus infection (COVID-19) is acute kidney injury (AKI). In the most seriously affected individuals, non-specific factors typical in chronically sick individuals, e.g., mechanical ventilation, hypoxia, hypotension, poor cardiac activity, and nephrotoxic drugs, may also be responsible for kidney damage and functional impairment [45]. According to a multivariate assessment, the frequency of AKI was correlated with male sex, black and Asian/Native American ethnicity, greater BMI, higher APACHE IV score [83], and lesser baseline estimated glomerular filtration rate (eGFR) [84]. Procalcitonin, C-reactive Protein, lactate dehydrogenase, serum ferritin, aspartate aminotransferase, fibrinogen, and reactive incomplete thromboplastin duration were among the laboratory factors linked to moderate-to-severe or severe AKI and the combined result in-hospital mortality [84].

Tubular damage is caused by low molecular mass proteinuria, Fanconi syndrome, histological abnormalities, and local inflammation. In addition, even after directly contracting a virus or compartment syndrome in the kidneys, administering antibiotics or antiviral drugs may be related to nephrotoxic-induced damage [45]. Another important aspect that might lead to acute kidney injury attributed to COVID-19 is vascular impairment. Endotheliitis, microthrombi, and thrombotic microangiopathy are the three factors that may lead to vascular impairment. As potential mediators of the pathophysiology and certain clinical signs of COVID-19, endothelial vascular impairment and thrombo inflammation related to SARS-CoV2 viral infections are now being identified [85]. Glomeruli are at the center of renal activity, even though they make up just a small portion of a complete nephron. When it comes to preserving homeostasis, they are invaluable. Acute interstitial nephritis and immune cell infiltration are the two conditions that lead to interstitial injury. In the documented kidney biopsy reports from individuals with COVID-19, interstitial infiltrates have not

often been noted [86]. However, according to research, most ICU individuals with severe COVID-19 likely take many drugs linked to interstitial nephritis [87].

5. Various Phases of COVID-19-Associated Acute Kidney Injury

Acute kidney injury linked to COVID-19 can be separated into three stages.(AKI stage-1, AKI stage-2, AKIstage-3). AKI stage 1 involves three substages (i.e., 1S, 1A, and 1B). Stage 1S designates a preliminary stage where evidence shows kidney injury occurs but is not picked up by creatinine and urine output parameters; in this stage, biomarkers of kidney injury give positive results, but there is no change in serum creatinine level and urine output (neither increase nor decrease) [88]. In AKI stage 1A, there is an increased serum creatinine (sCr) or decreased level of urine output (UO) but a negative result in biomarkers; in AKI stage 1B, there is an increased serum creatinine or decreased level of urine output with a positive result in biomarkers [88]. Patients with early-stage AKI may be identified via proteinuria detection [94]. The role of CKD is uncertain, but The percentage of individuals with proteinuria and COVID-19 is significantly higher than the frequency of stage 1 and stage 2 CKD in the general population [85]. AKI stage 2 involves two substages (i.e., 2A and 2B). There is a rise in sCr levels of more than 200% and a UO level of lower than 0.5 mL/kg/h for more than 12 hours in this substage, but 2A has a negative Biomarker, and 2B has a positive Biomarker. AKI stage 3 can also involve two substages (i.e., 3A and 3B). There is a rise in sCr levels of more than 300% and UO levels of lower than 0.5 mL/kg/h for more than 24 hours or Anuria for more than 12h in this substage, but 3A has a negative Biomarker, and 3B have positive Biomarker [88]. Analysis of post-mortem kidney samples from patients with stage 2 or stage 3 AKI and COVID-19 indicated acute tubular damage, which is characterized by mostly moderate localized acute tubular necrosis [86]. AKI stage 3 with COVID-19 patients is common and they carry high mortality rate. The majority of AKI stage 3 patients require kidney replacement therapy on mechanical ventilation, and 90% of individuals with stage 3 AKI who were not dialyzed died [87]. Reduced vasodilation, a pro-inflammatory environment, and prothrombotic characteristics are key features of endothelial dysfunction. Patients with SARS-CoV2 infection may experience coagulation impairment for various reasons. Two basic approaches might be used to summarize them Inflammation and cytokines storm and specific-virus mechanism where "cytokine storm" seems to play a pivotal role in virus-specific mechanisms, linked to the virus's interaction with the RAS and the fibrinolytic pathway, as well as comorbidities that these individuals have [88]. Possibly another virus-specific mechanism may be associated with autoimmunity development [94].

The cytokine storm may accelerate AKI in COVID-19

patients, By collaborating with renal resident cells and encouraging tubular and endothelial dysfunction [90]. The activation of innate immunity led to increased levels of many proinflammatory cytokines during the SARS-CoV2 infection. and the most severe symptoms of the illness appear to be caused by the so-called "cytokine release syndrome" [91], Interleukin-6 (IL-6) has emerged as one of these cytokines with a key function, and it is now being studied in therapeutic trials using anti-IL-6 medicines to treat severe forms [92]. In individuals with acute inflammatory diseases, such as sepsis and a hyper-coagulable state, elevated levels of tumor necrosis factor (TNF), IL-6, and IL-1 are detected in vivo, occasionally developing into DIC. Results from clinical trials indicate that IL-6 is the key player in cytokine-induced coagulation activation [93].

Additionally, IL-6 encourages the production of additional coagulation factors, including factor VIII and fibrinogen [94, 95], releases proinflammatory chemokines and cytokines by renal endothelial cells, and, through boosting VEGF release, acts on endothelial cells to cause vascular permeability [96, 97]. Additionally, pro-inflammatory cytokines can cause capillary leak syndrome and thrombosis formation, which might lead to disseminated intravascular coagulation [98]. According to reports, COVID-19 individuals have unusually high levels of the soluble IL-6 receptor (IL-6R) in their plasma as a result of the infection's accelerated cell surface cleavage; after then, most cells, including endothelial cells, can be directly activated by circulating complexes of soluble IL-6 and IL-6R [99]. The ongoing coagulopathy brought on by infection may also contribute to thrombocytopenia, and the cytokine storm may also encourage the growth of megakaryocytes, which would lead to thrombocytosis [100]. Additionally, because cytokines can activate macrophages, erythro-phagocytosis and Anemia are seen, Anemia, cytokine-induced injuries, and disruptions of vascular hemostasis all work in concert to cause renal multi-organ failure [101].

6. The Immune and Inflammatory Response of the Kidney Due to COVID-19

The primary symptoms of COVID-19 are hypoxia and respiratory distress; however, kidney involvement also occurs frequently. Presumably, there are several ways that viruses can infect the kidneys. Viruses can build up and sprout in glomeruli, where they may directly harm the host tissue. Furthermore, tissue antigens can passively elicit reactions, and viruses can function as a local stimulant to predispose the kidneys to microbial infection. According to contemporary research, the coronavirus penetrates cells via ACE2 and stimulates Toll-like receptors (TLRs) [107]. TLRs may induce the activation of transcriptional regulators, control the production of cytokines and chemokines that promote inflammation and contribute to the innate immune reaction. It has been suggested that these receptors are crucial

for the pathogenesis of kidney disease [107]. Mainly AKI (Acute Kidney Injury) is linked to overstimulation of these receptors. The precise location of ACE2 and transmembrane protease serine (TMPRSS) activity and distribution in kidney cells were determined in a recent study using single-cell RNA sequencing analysis [14]. Numerous mechanisms influence COVID-19-induced kidney damage, involving direct kidney damage caused by the virus and angiotensin-converting enzyme 2, aberrant immune response, a cytokine storm triggered by SARS-CoV-2 infection, organ linkages, a hypercoagulable condition, and endothelial malfunction.

Being infected with SARS-CoV-2, individuals with severe COVID-19 had considerably higher levels of neutrophils, leukocytes, and neutrophil-lymphocyte ratios than individuals with moderate COVID-19 [108]. Furthermore, individuals with COVID-19 who undergo kidney biopsy show significant amounts of CD4+ T cells, CD56+ natural killer cells, and CD68+ macrophages infiltrating the tubulointerstitial [109]. This situation denotes the activation of T lymphocytes, which then go toward the infection site to carry out their role. Nevertheless, SARS-CoV-2 targets tissues with an incompetent immune reaction and releases cytokine storms that cause T cells to necrotize or apoptosis, which diminishes T cells and hinders viral removal [21, 110]. As a result, individuals with COVID-19 are reported to have reduced lymphocyte levels and frequently have poor prognoses [111].

Furthermore, Immunoglobulin M (IgM), which binds ACE2 in kidney cells, is produced after SARS-CoV-2 infection and causes type 2 hypersensitivity responses, which drive kidney damage [109]. Several investigations using renal biopsies from COVID-19 individuals demonstrate the role of autoimmunity on renal activity. IgG, IgM, and C3 accumulation were found in the glomerular filtration barrier of COVID-19 patients [112]. After thoroughly analyzing kidney samples from COVID-19 individuals, Macor *et al.* noticed IgG and C aggregates surrounding the tubules and glomeruli [113]. Correspondingly, research reveals IgA granular accumulation in the renal mesangium of COVID-19 individuals through immunofluorescence and the demise of podocytes under electron microscopy. The study hypothesized that these pathological alterations were linked to type 3 hypersensitivity reactivity brought on by antigen-antibody complexes [114].

Anti-ACE2 autoantibodies in individuals can potentially disrupt the balance of ACE to ACE2, which might result in abnormalities of the renin-angiotensin system (RAS), promote tissue deterioration, and exacerbate inflammation [110]. Additionally, the complement system has a role in the pathophysiology of AKI in COVID-19 [115]. According to previous research, complement C5b-9 builds up at the brush borders of the apical tubules via a different mechanism after amassing in the lumen of the renal tubules, causing tubulointerstitial degeneration [116, 117]. According to an investigation, significant complement accumulation was seen on the renal tubules of six critically sick COVID-19 individuals whose kidneys were biopsied. This finding suggests that SARS-

CoV-2 infection might trigger complement accumulation and contribute to renal damage [115].

Furthermore, increased cytokines mediate inflammatory cells adhering to the kidney's endothelial cells, which might affect the kidneys [118]. A dysregulated RAS is associated with developing a cytokine storm [109]. The renin-angiotensin system's major enzyme, ACE2, transforms angiotensin I (Ang I) to Ang (1-9) and downregulates angiotensin II (Ang II) to Ang (1-7), which SARS-CoV-2 recognizes as a major receptor [119]. Ang II significantly impacts RAS via functioning on the AT1R and AT2R [109]. Between the two, Ang II activates AT1R, which is crucial for fluid balancing since it controls aldosterone secretion in the adrenal cortex. Furthermore, activating the AT1R can enhance thrombosis, inflammation, and fibrosis [120]. NF-κB, prostaglandins, vascular endothelial cell growth factor, TNF-α, IL-1b, IL-6, and IFN-g are just a few examples of the proinflammatory substances produced when Ang II combines with kidney resident cells [121, 122]. Additionally, it increases the cytokine/chemokine synthesis, which attracts immune cells (such as neutrophils, mononuclear cells, T cells, and B cells) to the damage location and intensifies the inflammatory reaction [123]. These components encourage kidney and endothelial malfunction, which results in AKI in COVID-19 patients. The solution will lie in addressing RAS abnormalities.

7. Similarities to Non-COVID-19 AKI with COVID-19 AKI

AKI in individuals with COVID-19 and AKI in sepsis unrelated to COVID have commonalities and distinctions histopathological studies have emphasized. The degree of similarity between sepsis-associated AKI and COVID-19 AKI is intriguing.

***Table 1.** Similarities between non-COVID-19 AKI and COVID-19 AKI.*

Similar categories	Non-COVID-19 AKI (Sepsis-associated AKI)	COVID-19 AKI	References
Glomerular filtration rate (GFR)	Dropped	Dropped	[45, 124]
Renal blood flow	Higher/Normal	Higher/Normal	[45, 124]
Regional inflammation	Occurred	Occurred	[45]
Microvascular abnormalities	Occurred	Occurred	[45]
Glomerular shunting	Altered	Altered	[125, 126]
Tubuloglomerular response stimulation	Altered	Altered	[125, 126]
Endothelial injury	Occurred	Occurred	[127, 128]
The penetrability of filtration barriers	Increased	Increased	[127, 128]
Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular proteins (DAMPs)	Involved	Involved	[2, 129]

A secondary effect of severe COVID-19 is acute respiratory distress syndrome (ARDS). Furthermore, there are additional variables linked to ARDS, such as hypoxemia, which can worsen renal vascular impedance, and raised central venous stress carried on by right-sided cardiac arrest, high intrathoracic pressures, or pulmonary vascular thrombi that can worsen interstitial and tubular hydrostatic pressure inside the encapsulated kidney, impairing renal blood flow and GFR in case of both non COVID-19 AKI and COVID-19 AKI [46, 130, 131].

8. Early Diagnosis and Drug Management Strategy of AKI in COVID-19

The kidney is an irreplaceable metabolic organ of our body. Several reasons play a crucial role in causing AKI. For example, heart failure, sepsis, hemorrhage, COVID-19, etc. [132]. AKI has become a commonly associated issue with COVID-19 infection [62, 63]. In severe cases, almost half of the individuals (having AKI associated) require kidney replacement [132, 133]. Furthermore, AKI mediated by COVID-19 is closely related to a higher death rate and health problems when it is progressed. Consequently, early detection offers a crucial therapeutic window for managing AKI to stop the development of chronic renal failure [64, 132].

Several factors are considered potential indicators for the early diagnosis of AKI. Treatment is currently utilizing urine output and creatinine level as an indicator of diagnosing AKI in its early stage [132]. Serum creatinine (SCR) is typically used to evaluate renal function. But it is not an efficient marker of early diagnosis of AKI. It previously shows glomerular activities but cannot pinpoint acute kidney damage [134, 135]. SCR is also unspecific in detecting AKI by COVID-19. In addition, several non-renal markers also cause a rise in the SCR level. One example: certain drugs (cimetidine, trimethoprim) can increase SCR levels in an average person [136].

Early AKI diagnosis has come a long way in recent years. Many potential markers have been proposed to detect AKI very early. One is KIM-1 (Kidney injury molecule-1), a possible early feature of acute renal disease, a characteristic glycoprotein primarily found in the renal tubular epithelium [137]. SARS-CoV-2 uses the ACE-2 receptor as its primary media to invade the cell. ACE-2 receptor is expressed mainly in renal tubular epithelial cells [57]. Podocyte malfunction, acute proximal tubular disruption, and necrosis can all arise from virus inclusion. As a result, KIM-1 level is upregulated and found in urine samples within 24 hours after AKI induced by COVID-19 [135, 137].

GGT (γ-glutamyl transpeptidase) is an enzyme. A tubular brush border enzyme is attached to the cytoplasmic membrane's external layer. Evidence suggests a surge in GGT level when renal kidney epithelial cells are damaged as an early diagnostic biomarker of AKI. A multiplex optical analysis method called MUR1-3 is used to identify several connected biomarkers (with GGT) that can help with the early diagnosis of AKI [132, 138].

Another early diagnostic marker, NAG (N-acetyl-ß-glucosaminidase), is a lysosomal catalyst in renal proximal tubule cells. Moreover, NAG in the urine indicates tubular lesions, as only highly modest levels of tubular indicators can be discovered in the urine of healthy individuals [135, 137]. The current study's findings demonstrate that KIM-1 may better identify AKI in COVID-19 patients than NAG. But then, additional research in a larger cohort is necessary for this purpose. SARS-CoV-2 mainly affects our respiratory system but is also responsible for many organ dysfunctions. Recent studies suggest the kidney is one of the target sites for COVID-19 inducing acute kidney injury [139]. Light and electron microscopy confirmed that SARS-CoV-2 had directly infected the kidneys [140]. Studies have shown that the ACE-2 receptor and 3CLpro receptor (3CL protease) play a fundamental role in the virus's life cycle. These two receptors are crucial because they serve as potential therapeutic targets to stop COVID-19 from progressing [141].

Several reports suggest that herbal remedies can be protective in the care of SARS-CoV-2 infected patients by halting the progression of COVID-19. A promising antiviral drug that might stop the coronavirus invasion through various signaling pathways is quercetin, a naturally occurring flavonoid plentiful [142]. 3CLpro is a protease enzyme. It plays a significant role in the viral replication cycle. Inhibiting the activity of this enzyme is a method of stopping the COVID-19 invasion of kidney cells. In addition, quercetin affects thermal stability, a defining feature of 3CLpro, and halts the virus [143]. The entrance receptor of COVID-19 ACE-2 interacts with viral spike protein and induces assimilation of the virus resulting in cytokine storm and inflammation. COVID-19 invasion of kidney cells can be stopped by using quercetin as an agent that can bind with the active site of ACE-2 [144]. Another study suggests it can prevent viral spike protein from interacting with certain areas [141, 145]. Present studies mark the protective role of quercetin in preventing AKI. However, further studies are needed to implement these theories into reality.

9. Treatment for COVID-19 AKI

Most information used to guide contemporary treatment methods or strategies for individuals with COVID-19 and acute kidney injury (AKI) comes from resource-rich circumstances, generally found in high-income nations. The implementation of these strategies in contexts with limited resources is frequently unfeasible. The regimen of COVID-19 individuals must involve testing for AKI, preventing AKI from developing or getting worse, and resolving AKI, including treating renal failure [146]. Depending on the etiology and intensity, AKI may require different treatments and preventive strategies. However, the ideal way to impede AKI in individuals with COVID-19 is yet unknown [146]. Preventative plans will be based on a growing comprehension of the mechanism of the disorder [147, 148]. Most contemporary AKI prevention strategies for COVID-19 individuals are premised on research on AKI in connection with infection and acute hypoxemic respiratory distress [149, 150]. A report showed that individuals with AKI died in hospitals at a substantially greater rate than those without AKI. In addition, AKI phase progression was linked to a rise in in-hospital fatality. According to records, individuals with phase III and those needing renal replacement treatment had the most incredible fatality rates [151].

Table 2. Some specific strategies for COVID-19 AKI with their advantages.

Strategies	Advantages	Reference
Avoidance of nephrotoxic drugs	Reduce the chance of developing glomerulonephritis Reduce the likelihood of developing inflammation in the proximal tubules Prevent the development of renal tissue fabrication	[152]
Regular assessment of urinary discharge and serum creatinine level	Indicate glomerular filtration rate Indicate any hindrance to urine abolishment Aids in spotting early indications of kidney damage.	[153]
Lung protective ventilation	Enhance kidney function Prevent hemodynamic shifts Reduce the sequences that cause the kidneys' stress from cytokines	[154]
Managing hypovolemia	Helps in the prevention of AKI Maintains appropriate concentrations of creatinine and urea in the blood Aids in preserving organ efficiency.	[155]
Renal replacements therapy (RRT)	Protect the organs and stop COVID-19 and AKI from spreading. Results in improving fluid equilibrium management and increasing hemodynamic consistency. RRT is more flexible and minimizes big changes and fluid changes.	[156]

If a conservative strategy is unsuccessful, renal replacements and extracorporeal assistance may be necessary [155]. Extracorporeal organ support (ECOS) and RRT will maintain the organs and stop the advancement of COVID-19 and AKI if they are started immediately [157]. Moreover, individuals with COVID-19 who are seriously sick frequently have a hypercoagulable condition. Hence extracorporeal circuit anticoagulation procedures should be utilized [158].

When respiratory fluxes worsen, extracorporeal membrane oxygenation is recommended [155]. Since clinical advancement might be rapid, applying successive extracorporeal treatments for immunomodulation, endotoxin and cytokine elimination, and extra-human organ support (ECOS) for different organs must be considered [107].

Table 3. *Different stages of AKI and their interventions.*

Conditions/Stage	Intervention	Mechanism	References
AKI	Drug: Vitamin C Drug: Control (Normal saline)	↓ reactive oxygen species (ROS) levels ↑ bioavailability	[159]
	Device: Renal Guard system	↑ urine flow rate ↓ toxic effect of contrast media	[160]
	Procedure: Fluid therapy During operation	↑ cardiac output and perfusion pressure ↑ renal blood flow and glomerular function	[161]
	Other: SUPPORT AKI Clinical Decision Support	↓ mortality for AKI patients	[162]
AKI I	Diagnostic test: Blood and Urine	↑ serum creatinine to 1.5-1.9 times from baseline	[163]
AKI II	Diagnostic test: Blood and Urine	↑ serum creatinine to 2.0-2.9 times from baseline	[163]
AKI III	Diagnostic test: Blood and Urine	↑ serum creatinine to ≥3.0 times from baseline	[163]

(note: ↓ = Decreased/Reduced, ↑ = Increased)

9.1. Renal Replacement Therapy

In 1946 Wilhelm Kolf did successful dialysis of a patient. It paved a revolutionary way to treat AKI and reduction of the death rate due to AKI. Despite a debate, it has become an indisputable method to treat acute kidney injury [156]. In the recent worldwide pandemic, COVID-19 has emerged as one of the main culprits for emerging respiratory disease outbreaks. But recent studies have shown that AKI is incorporated with COVID-19 [62]. In intensive care units (ICUs), 20–25% of patients suffering from acute kidney damage (AKI) need renal replacement therapy (RRT) [164]. Since it can eradicate different cytokines, endotoxins, or other toxic chemicals from the human body, it could become a potential treatment [165].

Kidney Disease Improving Global Outcomes (KDIGO) 2012 guideline 5.6.1. suggests using continuous RRT (CRRT) and intermittent RRT as supplemental therapy in AKI individuals because of some adverse effects of RRT that inhibit recovery from AKI. Therefore, the nephrologist providing RRT to severely sick patient with AKI must select the RRT technique that maximizes survivability without continuing AKI [161, 166].

Patients in severe situations frequently encounter substantial losses in both macro- and micronutrients. CRRT maintains the nutritional status of these patients by inhibiting more upset and regaining lean body mass with a positive nitrogen balance [167].

In COVID-19 victims, there is currently no way to evaluate cytokine levels immediately. Still, CKRT can be employed to non-selectively cleanse inflammatory cytokines from the body through dispersion, adsorption, and dispersion. Again, some young patients endure intense stress and elevated catabolism in AKI. CKRT controls this instability by providing hemodynamic stability by maintaining fluid balance [161, 167]. There is evidence that individuals treated with CKRT showed a noticeable decline in mortality rate compared to those who weren't treated with CKRT (54.5 vs. 74.6%, p = 0.032) [168]. However, CKRT has some disadvantages, for example: costly (around INR 25,000 to 30,000 daily for the average adult), sterilized fluid bags and unique filter sets, and patient immobilization [161]. On the other hand, some studies also suggest that early RRT commencement may increase survival time and provide essential therapy opportunities. As a result, they are reducing all-cause in-hospital mortality. The underlying mechanisms, though, are not yet completely understood [165]. Further studies are needed in this process to know about its advantage and disadvantage.

9.2. COVID-19 Studies in Kidney Transplant Recipients

A frequent issue, Acute Kidney Injury (AKI), in kidney transplantation, can occur in the donor before organ harvesting and the receiver soon after transplantation. It is either de novo post-transplant acute worsening of graft function or delayed graft function (DGF) [169]. Opportunistic infections after transplantation in kidney transplant recipients are typically brought on by viruses, which increase death rates and morbidity [37, 170]. After a kidney transplant, the risk of developing a viral infection is increased by various factors such as immune suppression, graft rejection, and tissue damage [37, 170].

According to a case study, kidney transplant recipients exhibit symptoms comparable to those seen in the general community during a pandemic [171]. Lymphopenia, hypoxia, chest crepitation, and elevated C-reactive Protein are some additional clinical signs that could appear in kidney transplant patients reported in the first 10 confirmed cases of COVID-19 among kidney transplant recipients [172]. The symptoms of COVID-19 can present many different forms, and the prognosis might vary greatly among kidney transplant recipients, but unfortunately, mortality is high in general [172]. Five patients with non-"severe" infections were included in a Chinese study of COVID-19 recipients

who received kidney transplants but did not experience mortality [173]. An additional Italian investigation on kidney transplant recipients with COVID-19 reported a 25% overall death rate among hospitalized patients [174]. Therefore, in-depth research is required to evaluate the mortality risk associated with transplant recipients carrying COVID-19 [172].

10. Conclusion

Patients with COVID-19 frequently have kidney involvement, ranging from proteinuria and hemorrhage to acute kidney injury (AKI), needing renal replacement treatment (RRT; also known as kidney replacement therapy). In addition, high mortality is linked to COVID-19-associated AKI (COVID-19 AKI), which acts as a risk factor for all-cause hospital death in COVID-19 patients. Therefore, the putative underlying processes of SARS-CoV2-induced kidney injury are highlighted in the current review. AKI's pathophysiology can be connected to both COVID-specific and non-specific pathways. Regional inflammation has a role in the organ destruction caused by COVID-19, and current research suggests that steroids and IL-6 receptor antagonists may effectively prevent severe AKI. However, more studies are needed to confirm these results and determine how they affect renal recovery. In various cohorts, including in examinations of tissue samples taken several weeks following disease start, a direct viral infection of kidney cells has been found. However, there are currently no treatment approaches that target the kidney, despite advances in understanding the mechanisms leading to renal disease in COVID-19. In addition, there is currently no established treatment for COVID-19-induced AKI. Therefore, more study is required to understand renal involvement better and develop diagnostic, prognostic, and therapeutic approaches for use in clinical settings.

References

[1] Guan, W.-j., et al., *Clinical Characteristics of Coronavirus Disease 2019 in China.* New England Journal of Medicine, 2020. 382 (18): p. 1708-1720.

[2] Batlle, D., et al., *Acute Kidney Injury in COVID-19: Emerging Evidence of a Distinct Pathophysiology.* J Am Soc Nephrol, 2020. 31 (7): p. 1380-1383.

[3] Cheng, Y., et al., *Kidney disease is associated with in-hospital death of patients with COVID-19.* Kidney Int, 2020. 97 (5): p. 829-838.

[4] Cheng, Y., et al., *The Incidence, Risk Factors, and Prognosis of Acute Kidney Injury in Adult Patients with Coronavirus Disease 2019.* Clin J Am Soc Nephrol, 2020. 15 (10): p. 1394-1402.

[5] Hirsch, J. S., et al., *Acute kidney injury in patients hospitalized with COVID-19.* Kidney Int, 2020. 98 (1): p. 209-218.

[6] Mohamed, M. M. B., et al., *Acute Kidney Injury Associated with Coronavirus Disease 2019 in Urban New Orleans.* Kidney360, 2020. 1 (7): p. 614-622.

[7] Cummings, M. J., et al., *Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study.* Lancet, 2020. 395 (10239): p. 1763-1770.

[8] Ng, J. H., et al., *Outcomes Among Patients Hospitalized With COVID-19 and Acute Kidney Injury.* Am J Kidney Dis, 2021. 77 (2): p. 204-215. e1.

[9] Nadim, M. K., et al., *COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup.* Nature Reviews Nephrology, 2020. 16 (12): p. 747-764.

[10] Gupta, S., et al., *Factors Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US.* JAMA Intern Med, 2020. 180 (11): p. 1436-1447.

[11] Murugan, R., et al., *Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival.* Kidney Int, 2010. 77 (6): p. 527-35.

[12] Ahmadian, E., et al., *COVID-19 and kidney injury: Pathophysiology and molecular mechanisms.* Reviews in medical virology, 2021. 31 (3): p. e2176-e2176.

[13] Khouchlaa, A. and A. Bouyahya, *COVID-19 nephropathy: probable mechanisms of kidney failure.* J Nephropathol, 2020. 9 (4): p. e35-e35.

[14] Pan, X. W., et al., *Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis.* Intensive Care Med, 2020. 46 (6): p. 1114-1116.

[15] Diao, B., et al., *Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 infection.* Nat Commun, 2021. 12 (1): p. 2506.

[16] Malha, L., et al., *COVID-19 and the Renin-Angiotensin System.* Kidney Int Rep, 2020. 5 (5): p. 563-565.

[17] Tolouian, R., et al., *COVID-19 interactions with angiotensin-converting enzyme 2 (ACE2) and the kinin system; looking at a potential treatment.* J Renal Inj Prev, 2020. 9 (2): p. e19-e19.

[18] Ciotti, M., et al., *The COVID-19 pandemic.* Crit Rev Clin Lab Sci, 2020. 57 (6): p. 365-388.

[19] Andersen, K. G., et al., *The proximal origin of SARS-CoV-2.* Nat Med, 2020. 26 (4): p. 450-452.

[20] Nao, N., et al., *Genetic Predisposition To Acquire a Polybasic Cleavage Site for Highly Pathogenic Avian Influenza Virus Hemagglutinin.* mBio, 2017. 8 (1).

[21] Huang, C., et al., *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.* Lancet, 2020. 395 (10223): p. 497-506.

[22] Yuki, K., M. Fujiogi, and S. Koutsogiannaki, *COVID-19 pathophysiology: A review.* Clin Immunol, 2020. 215: p. 108427.

[23] Shi, H., et al., *Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study.* Lancet Infect Dis, 2020. 20 (4): p. 425-434.

[24] Dhama, K., et al., *Coronavirus Disease 2019-COVID-19.* Clinical Microbiology Reviews, 2020. 33 (4): p. e00028-20.

[25] Channappanavar, R., J. Zhao, and S. Perlman, *T cell-mediated immune response to respiratory coronaviruses.* Immunol Res, 2014. 59 (1-3): p. 118-28.

[26] Rabi, F. A., et al., *SARS-CoV-2 and Coronavirus Disease 2019: What We Know So Far.* Pathogens, 2020. 9 (3).

[27] Bosch, B. J., et al., *The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex.* J Virol, 2003. 77 (16): p. 8801-11.

[28] Li, W., et al., *Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus.* Nature, 2003. 426 (6965): p. 450-4.

[29] Chen, Y., et al., *Structure analysis of the receptor binding of 2019-nCoV.* Biochem Biophys Res Commun, 2020. 525 (1): p. 135-40.

[30] Walls, A. C., et al., *Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein.* Cell, 2020. 181 (2): p. 281-292. e6.

[31] Letko, M., A. Marzi, and V. Munster, *Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses.* Nat Microbiol, 2020. 5 (4): p. 562-569.

[32] Zou, X., et al., *Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection.* Front Med, 2020. 14 (2): p. 185-192.

[33] Drosten, C., et al., *Identification of a novel coronavirus in patients with severe acute respiratory syndrome.* N Engl J Med, 2003. 348 (20): p. 1967-76.

[34] Alimohamadi, Y., et al., *Determine the most common clinical symptoms in COVID-19 patients: a systematic review and meta-analysis.* J Prev Med Hyg, 2020. 61 (3): p. E304-e312.

[35] Naicker, S., et al., *The Novel Coronavirus 2019 epidemic and kidneys.* Kidney Int, 2020. 97 (5): p. 824-828.

[36] Dadson, P., et al., *Underlying Kidney Diseases and Complications for COVID-19: A Review.* Front Med (Lausanne), 2020. 7: p. 600144.

[37] Yang, X., et al., *Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study.* Lancet Respir Med, 2020. 8 (5): p. 475-481.

[38] Anderson, R. M., et al., *How will country-based mitigation measures influence the course of the COVID-19 epidemic?* Lancet, 2020. 395 (10228): p. 931-934.

[39] Guo, Y. R., et al., *The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status.* Mil Med Res, 2020. 7 (1): p. 11.

[40] Yu, N., et al., *Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study.* Lancet Infect Dis, 2020. 20 (5): p. 559-564.

[41] Zheng, X., Y. Zhao, and L. Yang, *Acute Kidney Injury in COVID-19: The Chinese Experience.* Semin Nephrol, 2020. 40 (5): p. 430-442.

[42] Chong, W. H. and B. K. Saha, *Relationship Between Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the Etiology of Acute Kidney Injury (AKI).* Am J Med Sci, 2021. 361 (3): p. 287-296.

[43] Smarz-Widelska, I., et al., *Pathophysiology and Clinical Manifestations of COVID-19-Related Acute Kidney Injury-The Current State of Knowledge and Future Perspectives.* Int J Mol Sci, 2021. 22 (13).

[44] Bonventre, J. V. and L. Yang, *Cellular pathophysiology of ischemic acute kidney injury.* J Clin Invest, 2011. 121 (11): p. 4210-21.

[45] Legrand, M., et al., *Pathophysiology of COVID-19-associated acute kidney injury.* Nat Rev Nephrol, 2021. 17 (11): p. 751-764.

[46] Ng, J. H., et al., *Pathophysiology and pathology of acute kidney injury in patients with COVID-19.* Advances in Chronic Kidney Disease, 2020. 27 (5): p. 365-376.

[47] Xia, P., et al., *Clinicopathological features and outcomes of acute kidney injury in critically ill COVID-19 with prolonged disease course: a retrospective cohort.* Journal of the American Society of Nephrology, 2020. 31 (9): p. 2205-2221.

[48] Santoriello, D., et al., *Postmortem kidney pathology findings in patients with COVID-19.* Journal of the American Society of Nephrology, 2020. 31 (9): p. 2158-2167.

[49] Sharma, P., et al., *COVID-19–associated kidney injury: a case series of kidney biopsy findings.* Journal of the American Society of Nephrology, 2020. 31 (9): p. 1948-1958.

[50] Ferlicot, S., et al., *The spectrum of kidney biopsies in hospitalized patients with COVID-19, acute kidney injury and/or proteinuria.* Nephrology Dialysis Transplantation, 2021. 36 (7): p. 1253-1262.

[51] Hanif MO, B. A., Ramphul K, *Acute Renal Tubular Necrosis.* StatPearls 2022 Jan.

[52] Karakala, N. and A. J. Tolwani, *Timing of renal replacement therapy for acute kidney injury.* Journal of Intensive Care Medicine, 2019. 34 (2): p. 94-103.

[53] Ye, Q., B. Wang, and J. Mao, *The pathogenesis and treatment of theCytokine Storm'in COVID-19.* Journal of infection, 2020. 80 (6): p. 607-613.

[54] Larsen, C. P., et al., *Collapsing glomerulopathy in a patient with COVID-19.* Kidney international reports, 2020. 5 (6): p. 935.

[55] Nasr, S. H. and J. B. Kopp, *COVID-19–associated collapsing glomerulopathy: an emerging entity.* Kidney international reports, 2020. 5 (6): p. 759.

[56] D'Agati, V. D., F. J. Kaskel, and R. J. Falk, *Focal segmental glomerulosclerosis.* New England Journal of Medicine, 2011. 365 (25): p. 2398-2411.

[57] Velez, J. C. Q., T. Caza, and C. P. Larsen, *COVAN is the new HIVAN: the re-emergence of collapsing glomerulopathy with COVID-19.* Nature Reviews Nephrology, 2020. 16 (10): p. 565-567.

[58] Delsante, M., et al., *Kidney Involvement in COVID-19: Need for Better Definitions.* J Am Soc Nephrol, 2020. 31 (9): p. 2224-2225.

[59] Jain, U., *Effect of COVID-19 on the Organs.* Cureus, 2020. 12 (8): p. e9540.

[60] Han, X. and Q. Ye, *Kidney involvement in COVID-19 and its treatments.* J Med Virol, 2021. 93 (3): p. 1387-1395.

[61] Chen, N., et al., *Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study.* Lancet, 2020. 395 (10223): p. 507-513.

[62] Richardson, S., et al., *Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area.* Jama, 2020. 323 (20): p. 2052-2059.

[63] Wang, D., et al., *Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China.* Jama, 2020. 323 (11): p. 1061-1069.

[64] Guzik, T. J., et al., *COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options.* Cardiovasc Res, 2020. 116 (10): p. 1666-1687.

[65] Wang, L., et al., *Coronavirus Disease 19 Infection Does Not Result in Acute Kidney Injury: An Analysis of 116 Hospitalized Patients from Wuhan, China.* Am J Nephrol, 2020. 51 (5): p. 343-348.

[66] Gabarre, P., et al., *Acute kidney injury in critically ill patients with COVID-19.* Intensive Care Medicine, 2020. 46 (7): p. 1339-1348.

[67] Laghlam, D., M. Jozwiak, and L. S. Nguyen, *Renin-Angiotensin-Aldosterone System and Immunomodulation: A State-of-the-Art Review.* Cells, 2021. 10 (7).

[68] Schneider, W. M., et al., *Genome-Scale Identification of SARS-CoV-2 and Pan-coronavirus Host Factor Networks.* Cell, 2021. 184 (1): p. 120-132. e14.

[69] Deshotels, M. R., et al., *Angiotensin II mediates angiotensin converting enzyme type 2 internalization and degradation through an angiotensin II type I receptor-dependent mechanism.* Hypertension, 2014. 64 (6): p. 1368-1375.

[70] Zhou, F., et al., *Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.* Lancet, 2020. 395 (10229): p. 1054-1062.

[71] Su, H., C. T. Lei, and C. Zhang, *Interleukin-6 Signaling Pathway and Its Role in Kidney Disease: An Update.* Front Immunol, 2017. 8: p. 405.

[72] Valizadeh, R., et al., *Coronavirus-nephropathy; renal involvement in COVID-19.* J Renal Inj Prev, 2020. 9 (2): p. e18.

[73] Kapp, M. E., et al., *Renal Considerations in COVID-19: Biology, Pathology, and Pathophysiology.* Asaio Journal, 2021. 67 (10): p. 1087.

[74] Khan, S., et al., *Does SARS-CoV-2 infect the kidney?* Journal of the American Society of Nephrology, 2020. 31 (12): p. 2746-2748.

[75] Fogagnolo, A., et al., *Focus on renal blood flow in mechanically ventilated patients with SARS-CoV-2: a prospective pilot study.* J Clin Monit Comput, 2022. 36 (1): p. 161-167.

[76] Vasquez-Bonilla, W. O., et al., *A review of the main histopathological findings in coronavirus disease 2019.* Hum Pathol, 2020. 105: p. 74-83.

[77] Bowe, B., et al., *Acute Kidney Injury in a National Cohort of Hospitalized US Veterans with COVID-19.* Clin J Am Soc Nephrol, 2020. 16 (1): p. 14-25.

[78] Legrand, M., et al., *When cardiac failure, kidney dysfunction, and kidney injury intersect in acute conditions: the case of cardiorenal syndrome.* Crit Care Med, 2014. 42 (9): p. 2109-17.

[79] Kawakami, R., et al., *Pathological Evidence for SARS-CoV-2 as a Cause of Myocarditis: JACC Review Topic of the Week.* J Am Coll Cardiol, 2021. 77 (3): p. 314-325.

[80] Grasselli, G., et al., *Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy.* Jama, 2020. 323 (16): p. 1574-1581.

[81] Guan, W. J. and N. S. Zhong, *Clinical Characteristics of COVID-19 in China. Reply.* N Engl J Med, 2020. 382 (19): p. 1861-1862.

[82] Panitchote, A., et al., *Factors associated with acute kidney injury in acute respiratory distress syndrome.* Annals of Intensive Care, 2019. 9 (1): p. 74.

[83] Zimmerman, J. E., et al., *Intensive care unit length of stay: Benchmarking based on Acute Physiology and Chronic Health Evaluation (APACHE) IV.* Crit Care Med, 2006. 34 (10): p. 2517-29.

[84] El Mouhayyar, C., et al., *Factors Associated with Severity of Acute Kidney Injury and Adverse Outcomes in Critically Ill Patients with COVID-19.* Nephron, 2022: p. 1-9.

[85] Levy, J. H., T. Iba, and E. E. Gardiner, *Endothelial Injury in COVID-19 and Acute Infections: Putting the Pieces of the Puzzle Together.* Arterioscler Thromb Vasc Biol, 2021. 41 (5): p. 1774-1776.

[86] Rossi, G. M., et al., *Kidney Biopsy Findings in a Critically Ill COVID-19 Patient With Dialysis-Dependent Acute Kidney Injury: A Case Against "SARS-CoV-2 Nephropathy."* Kidney Int Rep, 2020. 5 (7): p. 1100-1105.

[87] Szajek, K., et al., *Granulomatous interstitial nephritis in a patient with SARS-CoV-2 infection.* BMC Nephrol, 2021. 22 (1): p. 19.

[88] Ostermann, M., et al., *Recommendations on acute kidney injury biomarkers from the acute disease quality initiative consensus conference: a consensus statement.* JAMA network open, 2020. 3 (10): p. e2019209-e2019209.

[89] Werion, A., et al., *SARS-CoV-2 causes a specific dysfunction of the kidney proximal tubule.* Kidney international, 2020. 98 (5): p. 1296-1307.

[90] Gansevoort, R. T., et al., *Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention.* The Lancet, 2013. 382 (9889): p. 339-352.

[91] Su, H., et al., *Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China.* Kidney international, 2020. 98 (1): p. 219-227.

[92] Zahid, U., et al., *Acute kidney injury in COVID-19 patients: an inner city hospital experience and policy implications.* American journal of nephrology, 2020. 51 (10): p. 786-796.

[93] Lazzaroni, M. G., et al., *Coagulation dysfunction in COVID-19: the interplay between inflammation, viral infection and the coagulation system.* Blood reviews, 2021. 46: p. 100745.

[94] Goeijenbier, M., et al., *Viral infections and mechanisms of thrombosis and bleeding.* Journal of medical virology, 2012. 84 (10): p. 1680-1696.

[95] Pei, G., et al., *Renal involvement and early prognosis in patients with COVID-19 pneumonia.* Journal of the American Society of Nephrology, 2020. 31 (6): p. 1157-1165.

[96] Mehta, P., et al., *COVID-19: consider cytokine storm syndromes and immunosuppression.* The lancet, 2020. 395 (10229): p. 1033-1034.

[97] Xu, X., et al., *Effective treatment of severe COVID-19 patients with tocilizumab.* Proceedings of the National Academy of Sciences, 2020. 117 (20): p. 10970-10975.

[98] Levi, M. and T. van der Poll, *Coagulation and sepsis.* Thrombosis research, 2017. 149: p. 38-44.

[99] Stirling, D., W. A. Hannant, and C. A. Ludlam, *Transcriptional activation of the factor VIII gene in liver cell lines by interleukin-6.* Thrombosis and haemostasis, 1998. 59 (01): p. 74-78.

[100] Stouthard, J. M., et al., *Interleukin-6 stimulates coagulation, not fibrinolysis, in humans.* Thrombosis and haemostasis, 1996. 76 (11): p. 738-742.

[101] Cohen, T., *Nahari D, Cerem LW, Neufeld G, Levi BZ.* Interleukin. 6: p. 736-741.

[102] Desai, T. R., et al., *Interleukin-6 causes endothelial barrier dysfunction via the protein kinase C pathway.* Journal of surgical research, 2002. 104 (2): p. 118-123.

[103] Henderson, L. A., et al., *On the alert for cytokine storm: immunopathology in COVID-19.* Arthritis & rheumatology, 2020. 72 (7): p. 1059-1063.

[104] Zunke, F. and S. Rose-John, *The shedding protease ADAM17: Physiology and pathophysiology.* Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 2017. 1864 (11): p. 2059-2070.

[105] Qu, R., et al., *Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19.* Journal of medical virology, 2020. 92 (9): p. 1533-1541.

[106] Mangalmurti, N. and C. A. Hunter, *Cytokine storms: understanding COVID-19.* Immunity, 2020. 53 (1): p. 19-25.

[107] Askari, H., et al., *Kidney diseases and COVID-19 infection: causes and effect, supportive therapeutics and nutritional perspectives.* Heliyon, 2021. 7 (1): p. e06008.

[108] Qin, C., et al., *Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China.* Clin Infect Dis, 2020. 71 (15): p. 762-768.

[109] He, W., et al., *Mechanisms of SARS-CoV-2 Infection-Induced Kidney Injury: A Literature Review.* Front Cell Infect Microbiol, 2022. 12: p. 838213.

[110] Chen, D., et al., *Hypokalemia and Clinical Implications in Patients with Coronavirus Disease 2019 (COVID-19).* medRxiv, 2020: p. 2020.02.27.20028530.

[111] Tan, L., et al., *Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study.* Signal Transduct Target Ther, 2020. 5 (1): p. 33.

[112] Winkler, A., et al., *SARS-CoV-2 infection and recurrence of anti-glomerular basement disease: a case report.* BMC Nephrol, 2021. 22 (1): p. 75.

[113] Macor, P., et al., *Multiple-Organ Complement Deposition on Vascular Endothelium in COVID-19 Patients.* Biomedicines, 2021. 9 (8).

[114] Jedlowski, P. M. and M. F. Jedlowski, *Coronavirus disease 2019-associated immunoglobulin A vasculitis/Henoch-Schönlein purpura: A case report and review.* J Dermatol, 2022. 49 (1): p. 190-196.

[115] Noris, M., A. Benigni, and G. Remuzzi, *The case of complement activation in COVID-19 multiorgan impact.* Kidney Int, 2020. 98 (2): p. 314-322.

[116] David, S., et al., *Alternative pathway complement activation induces proinflammatory activity in human proximal tubular epithelial cells.* Nephrol Dial Transplant, 1997. 12 (1): p. 51-6.

[117] Cybulsky, A. V., et al., *Complement C5b-9 membrane attack complex increases expression of endoplasmic reticulum stress proteins in glomerular epithelial cells.* J Biol Chem, 2002. 277 (44): p. 41342-51.

[118] He, Z., et al., *Effects of severe acute respiratory syndrome (SARS) coronavirus infection on peripheral blood lymphocytes and their subsets.* Int J Infect Dis, 2005. 9 (6): p. 323-30.

[119] Hoffmann, M., et al., *SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor.* Cell, 2020. 181 (2): p. 271-280. e8.

[120] Karnik, S. S., et al., *International Union of Basic and Clinical Pharmacology. XCIX. Angiotensin Receptors: Interpreters of Pathophysiological Angiotensinergic Stimuli [corrected].* Pharmacol Rev, 2015. 67 (4): p. 754-819.

[121] Williams, B., et al., *Angiotensin II increases vascular permeability factor gene expression by human vascular smooth muscle cells.* Hypertension, 1995. 25 (5): p. 913-7.

[122] Fyhrquist, F. and O. Saijonmaa, *Renin-angiotensin system revisited.* J Intern Med, 2008. 264 (3): p. 224-36.

[123] Nataraj, C., et al., *Angiotensin II regulates cellular immune responses through a calcineurin-dependent pathway.* J Clin Invest, 1999. 104 (12): p. 1693-701.

[124] Langenberg, C., et al., *Renal blood flow and function during recovery from experimental septic acute kidney injury.* Intensive Care Med, 2007. 33 (9): p. 1614-8.

[125] Joannidis, M., et al., *Neutrophil transmigration in renal proximal tubular LLC-PK1 cells.* Cell Physiol Biochem, 2004. 14 (1-2): p. 101-12.

[126] Bellomo, R., et al., *Acute kidney injury in sepsis.* Intensive Care Med, 2017. 43 (6): p. 816-828.

[127] Lerolle, N., et al., *Histopathology of septic shock induced acute kidney injury: apoptosis and leukocytic infiltration.* Intensive Care Med, 2010. 36 (3): p. 471-8.

[128] Bernardo, A., et al., *Effects of inflammatory cytokines on the release and cleavage of the endothelial cell-derived ultralarge von Willebrand factor multimers under flow.* Blood, 2004. 104 (1): p. 100-6.

[129] Delvaeye, M. and E. M. Conway, *Coagulation and innate immune responses: can we view them separately?* Blood, 2009. 114 (12): p. 2367-74.

[130] Darmon, M., et al., *Impact of mild hypoxemia on renal function and renal resistive index during mechanical ventilation.* Intensive Care Med, 2009. 35 (6): p. 1031-8.

[131] Legrand, M., et al., *Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study.* Crit Care, 2013. 17 (6): p. R278.

[132] Xiao, Z., et al., *Emerging early diagnostic methods for acute kidney injury.* Theranostics, 2022. 12 (6): p. 2963-2986.

[133] Wen, Y. and C. R. Parikh, *The Aftermath of AKI: Recurrent AKI, Acute Kidney Disease, and CKD Progression.* J Am Soc Nephrol, 2021. 32 (1): p. 2-4.

[134] Ronco, C., R. Bellomo, and J. A. Kellum, *Acute kidney injury.* The Lancet, 2019. 394 (10212): p. 1949-1964.

[135] Vogel, M. J., et al., *Kidney injury molecule-1: potential biomarker of acute kidney injury and disease severity in patients with COVID-19.* Journal of Nephrology, 2021. 34 (4): p. 1007-1018.

[136] Burwick, R. M., et al., *Differentiating Hemolysis, Elevated Liver Enzymes, and Low Platelet Count Syndrome and Atypical Hemolytic Uremic Syndrome in the Postpartum Period.* Hypertension, 2021. 78 (3): p. 760-768.

[137] Moresco, R. N., et al., *Urinary kidney injury molecule-1 in renal disease.* Clinica chimica acta, 2018. 487: p. 15-21.

[138] Cheng, P., et al., *Multiplex Optical Urinalysis for Early Detection of Drug-Induced Kidney Injury.* Anal Chem, 2020. 92 (8): p. 6166-6172.

[139] Lim, J. H., et al., *Fatal Outcomes of COVID-19 in Patients with Severe Acute Kidney Injury.* J Clin Med, 2020. 9 (6).

[140] Farkash, E. A., A. M. Wilson, and J. M. Jentzen, *Ultrastructural Evidence for Direct Renal Infection with SARS-CoV-2.* J Am Soc Nephrol, 2020. 31 (8): p. 1683-1687.

[141] Gu, Y. Y., et al., *Quercetin as a potential treatment for COVID-19-induced acute kidney injury: Based on network pharmacology and molecular docking study.* PLoS One, 2021. 16 (1): p. e0245209.

[142] Huang, Y. F., et al., *Review on the potential action mechanisms of Chinese medicines in treating Coronavirus Disease 2019 (COVID-19).* Pharmacol Res, 2020. 158: p. 104939.

[143] Abian, O., et al., *Structural stability of SARS-CoV-2 3CLpro and identification of quercetin as an inhibitor by experimental screening.* Int J Biol Macromol, 2020. 164: p. 1693-1703.

[144] Williamson, G. and A. Kerimi, *Testing of natural products in clinical trials targeting the SARS-CoV-2 (COVID-19) viral spike protein-angiotensin converting enzyme-2 (ACE2) interaction.* Biochem Pharmacol, 2020. 178: p. 114123.

[145] Vijayakumar, B. G., et al., *In silico pharmacokinetic and molecular docking studies of natural flavonoids and synthetic indole chalcones against essential proteins of SARS-CoV-2.* Eur J Pharmacol, 2020. 886: p. 173448.

[146] Rudd, K. E., et al., *Pragmatic Recommendations for the Prevention and Treatment of Acute Kidney Injury in Patients with COVID-19 in Low- and Middle-Income Countries.* Am J Trop Med Hyg, 2021. 104 (3_Suppl): p. 87-98.

[147] Puelles, V. G., et al., *Multiorgan and Renal Tropism of SARS-CoV-2.* N Engl J Med, 2020. 383 (6): p. 590-592.

[148] Soleimani, M., *Acute Kidney Injury in SARS-CoV-2 Infection: Direct Effect of Virus on Kidney Proximal Tubule Cells.* Int J Mol Sci, 2020. 21 (9).

[149] Ronco, C., T. Reis, and F. Husain-Syed, *Management of acute kidney injury in patients with COVID-19.* Lancet Respir Med, 2020. 8 (7): p. 738-742.

[150] Hassanein, M., G. Thomas, and J. Taliercio, *Management of acute kidney injury in COVID-19.* Cleveland Clinic Journal of Medicine, 2020.

[151] Diebold, M., et al., *Acute kidney injury in patients with COVID-19: a retrospective cohort study from Switzerland.* Swiss Med Wkly, 2021. 151: p. w20482.

[152] Kim, S. Y. and A. Moon, *Drug-induced nephrotoxicity and its biomarkers.* Biomol Ther (Seoul), 2012. 20 (3): p. 268-72.

[153] Gounden, V., H. Bhatt, and I. Jialal, *Renal Function Tests*, in *StatPearls*. 2022, StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.: Treasure Island (FL).

[154] Neves, P., et al., *Acute Kidney Injury Due to COVID-19 in Intensive Care Unit: An Analysis From a Latin-American Center.* Front Med (Lausanne), 2021. 8: p. 620050.

[155] Wishahi, M. and N. M. Kamal, *Multidisciplinary basic and clinical research of acute kidney injury with COVID-19: Pathophysiology, mechanisms, incidence, management and kidney transplantation.* World J Nephrol, 2022. 11 (3): p. 105-114.

[156] Lobo, V. A., *Renal Replacement Therapy in Acute Kidney Injury: Which Mode and When?* Indian J Crit Care Med, 2020. 24 (Suppl 3): p. S102-s106.

[157] Joannidis, M., et al., *Lung-kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup.* Intensive Care Med, 2020. 46 (4): p. 654-672.

[158] Husain-Syed, F., et al., *Extracorporeal organ support (ECOS) in critical illness and acute kidney injury: from native to artificial organ crosstalk.* Intensive Care Med, 2018. 44 (9): p. 1447-1459.

[159] Dennis, J. M. and P. K. Witting, *Protective role for antioxidants in acute kidney disease.* Nutrients, 2017. 9 (7): p. 718.

[160] Katoh, H., et al., *RenalGuard system to prevent contrast-induced acute kidney injury in Japanese patients with renal dysfunction; RESPECT KIDNEY study.* Cardiovascular intervention and therapeutics, 2019. 34 (2): p. 105-112.

[161] Ostermann, M., K. Liu, and K. Kashani, *Fluid management in acute kidney injury.* Chest, 2019. 156 (3): p. 594-603.

[162] Al-Jaghbeer, M., et al., *Clinical decision support for in-hospital AKI.* Journal of the American Society of Nephrology, 2018. 29 (2): p. 654-660.

[163] Ostermann, M. and M. Joannidis, *Acute kidney injury 2016: diagnosis and diagnostic workup.* Critical care, 2016. 20 (1): p. 1-13.

[164] Annigeri, R. A., et al., *Renal support for acute kidney injury in the developing world.* Kidney International Reports, 2017. 2 (4): p. 559-578.

[165] Qian, J., et al., *Early Renal-Replacement Therapy May Reduce the All-Cause Mortality of Severe COVID-19: An Observational Cohort Study.* Blood Purif, 2022: p. 1-9.

[166] Kellum, J. A., et al., *Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury.* Kidney international supplements, 2012. 2 (1): p. 1-138.

[167] Raina, R., et al., *Kidney replacement therapy in COVID-19 induced kidney failure and septic shock: a pediatric continuous renal replacement therapy [PCRRT] position on emergency preparedness with resource allocation.* Frontiers in pediatrics, 2020. 8: p. 413.

[168] Yang, Y., et al., *Effect of continuous renal replacement therapy on all-cause mortality in COVID-19 patients undergoing invasive mechanical ventilation: a retrospective cohort study.* MedRxiv, 2020.

[169] Palmisano, A., et al., *Acute Kidney Injury (AKI) before and after Kidney Transplantation: Causes, Medical Approach, and Implications for the Long-Term Outcomes.* J Clin Med, 2021. 10 (7).

[170] Cukuranovic, J., et al., *Viral infection in renal transplant recipients.* ScientificWorldJournal, 2012. 2012: p. 820621.

[171] Lubetzky, M., et al., *Kidney allograft recipients, immunosuppression, and coronavirus disease-2019: a report of consecutive cases from a New York City transplant center.* Nephrol Dial Transplant, 2020. 35 (7): p. 1250-1261.

[172] Nair, V., et al., *COVID-19 in kidney transplant recipients.* Am J Transplant, 2020. 20 (7): p. 1819-1825.

[173] Zhang, H., et al., *Identification of Kidney Transplant Recipients with Coronavirus Disease 2019.* Eur Urol, 2020. 77 (6): p. 742-747.

[174] Alberici, F., et al., *Management of Patients on Dialysis and With Kidney Transplantation During the SARS-CoV-2 (COVID-19) Pandemic in Brescia, Italy.* Kidney Int Rep, 2020. 5 (5): p. 580-585.