Recent Evidence on Acute Kidney Injury in COVID-19 Patients: A Narrative Review

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A B S T R A C T

The pandemic of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The clinical manifestation of COVID-19 is broad, ranging from an asymptomatic carrier state to severe disease leading to the death penalty. There is also emerging evidence that kidneys are affected early in COVID-19. Proteinuria and haematuria have been reported in 44% and 26.7% on admission, respectively. This literature review shows clinical manifestations of acute kidney injury (AKI) in a patient with COVID-19 infection. Literature reviews are carried out on various sources found on Google Scholar and Pubmed to search for articles, journal research, case reports, systematic reviews, meta-analyses, and textbooks. Various studies demonstrate the possibility of coronavirus infecting the kidney with several mechanisms such as cytokine storm syndrome (CSS), direct viral infection, and imbalance of renin-angiotensin-aldosterone (RAAS). Haematuria and proteinuria are associated with higher mortality and may signify aggressive disease early. Thus all patients should have a baseline urinalysis. There is a number of different causes of AKI in COVID-19, and some mechanisms by which COVID-19 affects kidneys remain unclear.

1. Introduction

In December 2019, pneumonia disease with unknown etiology was occurring in Wuhan, Hubei, China. The incidence increased significantly and spread rapidly to several countries in less than a month. This situation is known as coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1-4] Moreover, the World Health Organization (WHO) designated this incidence as a global pandemic on March 11, 2020.

There were 176,531,710 COVID-19 confirmed cases and 3,826,181 death reports around the world on June 17, 2020.[5]

The individuals who confirmed Covid infection usually experience mild to moderate symptoms. The most common clinical symptoms are fever, fatigue, and dry cough.[4,6,7] Meanwhile, some patients with comorbidities may experience multiorgan dysfunctions, particularly kidney involvement. Kidney

involvement is often found in hospitalized patients with COVID-19. Around 75% of patients were proteinuria, hematuria, and acute kidney injury (AKI).[8] Wang et al. reported that COVID-19 patients with acute respiratory disease symptoms (ARDS) were more prone to develop AKI.[9] While Werion et al. reported that proteinuria, hematuria, and elevation of serum creatinine were occurring in COVID-19 patients, which led to kidney injury.[1] Acute kidney injury (AKI) affected critically ill patients who were admitted to intensive care units in Europe and the United States (US) approximately 20–40%. Furthermore, early diagnosis of kidney involvement will prevent morbidity and mortality in patients.[10] This literature review was aimed to describe the correlation between acute kidney injury and COVID-19.

Pathophysiology of COVID-19

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The incubation period of the virus is 5-6 days up to 14 days. In severe cases of COVID-19, it can cause pneumonia, acute respiratory syndrome, kidney failure, and even death.[2,4,6]

The pathophysiology of COVID-19-infected humans is still unclear. In the early phase, the viral spike protein (S) attaches to the ACE-2 receptor. ACE receptors (ACE and ACE2) are found in almost all body tissues, but ACE-2 is dominant in type II alveolar epithelial cells and endothelial capillary cells. The SARS-CoV-2 infection causes reduced ACE2 function and increased angiotensin II levels. The activity of the renin-angiotensin-aldosterone system (RAAS) has an important role in kidney damage. Angiotensin II acts as a vasoconstrictor and activates the coagulation cascade by increasing platelet activation.[11]

Furthermore, in the next phase, viral replication increases, which develops epithelial-endothelial tissue barrier weak and damages the endothelial cell.[12] Endothelial injury is caused by mediated infection (elevation of von Willebrand factor level) and endotheliosis (neutrophils and macrophages presence).[2,8] This mechanism is found in several vascular layers (including the lungs, kidneys, heart, small intestine, and liver) in patients with COVID-19. This condition can trigger excessive thrombin production, inhibit fibrinolysis, and activate the complement pathway, which initiating thrombo-inflammation and ultimately leads to microthrombi deposition and microvascular dysfunction. Inflammation and edema occur due to the infiltration of mononuclear cells into the interstitial tissue, and it was founded on the ground-glass opacity in computed tomographic imaging (CT-Scan).[2]

In severe COVID-19 symptoms, the clinical manifestation of coagulation and blood clotting begins to appear. The study in Wuhan, China, reported that 71% of the 183 individuals who died from COVID-19 were found to have extensive intravascular coagulation.[2] Elevation of inflammatory markers such as C-reactive protein, ferritin, erythrocyte sedimentation rate, D-dimer, fibrinogen, and lactate dehydrogenase are predictors of critical illness and mortality in COVID-19 patients.[12]

Epidemiology of AKI in COVID-19 patients

Acute kidney injury (AKI) is a common complication in Covid-19 patients. The cases have been growing since then.[1,9,12] The incidence of COVID-19 patients with AKI in the ICU is 4.2% (94 cases). Meanwhile, the proportion of AKI in non-survival patients was 30%. Both of these data indicate a lower survival rate for COVID-19 patients with AKI complications.[8] The data by Zahid et al. reported that the incidence of AKI in COVID-19 patients ranged from 27-45% of cases. These situations appear when patients have high creatinine levels. In the critically ill patient with COVID-19, the incidence of AKI increases to 61-67%, as many as 31-66% of AKI patients experience AKI stage 3, and 14-55% of patients require Renal Replacement Therapy (RRT).[13]

Risk factors of kidney involvement in COVID-19
Age

The occurrence of coronavirus infection has

happened in the male gender (51.4%), aged 30-79 years old. As many as 81% of symptom cases were mild, 14% severe, and 5% critical.[15] Kohle et al. reported that increasing age in patients with COVID-19 raises the risk of AKI with a vulnerable age of 73 years. Meanwhile, another study found that those aged over 60 years had a more significant risk.[15] The elderly and people with comorbidities have a higher possibility of having severe symptoms than others because it is associated with mortality rates. The CDC reports that the case fatality rate (CFR) in patients aged 80 years is 14.8%, while the overall CFR is 2.3%. In Italy, the CFR of patients at the age of 80 was 20.2%, while the overall CFR was 7.2%.[1,6,13,15]

Race or ethnicity

Individuals of black and Asian races have a risk of developing AKI. Data from the Intensive Care National Audit and Research Center (ICNARC) reported that the mortality rate of COVID-19 patients admitted to the ICU was higher in black and Asian ethnicities.[13]

Comorbidities

Diabetes mellitus, hypertension, ischemic heart disease, and chronic kidney disease (CKD) are associated with micro and macrovascular complications in COVID-19 patients. A previous study reported the patient who had a history of diabetes mellitus with coronavirus infection was 41%-45%. According to Khole et al., comorbidity plays a significant aspect in the AKI incidence in COVID-19 patients.[8,13] The mortality rate was rising by the presence of comorbid diseases in the patient, namely cardiovascular disease (10.5%), diabetes (7.3%), chronic respiratory disease (6.3%), hypertension (6%), and 5.6% in patients with cancer.[6]

Haematuria and proteinuria are risk markers for ARDS, AKI, and increased mortality rate.[8] Therefore, a urinalysis in COVID-19 patients is required to determine the individual's risk factors.

Consuming nephrotoxic drugs. Remdesivir is an antiviral medicine that has a high cure rate with lower mortality in COVID-19 patients. It is not recommended

in patients with eGFR < 30 mL/min/1.73 m^2 because it excretes in the renal.[8]

The mechanism of acute kidney injury in COVID-19 patient

The are several theories about the relationship between COVID-19 and AKI. However, the exact causes remain unknown. Several studies assume several mechanisms, for instance, cytokine storm syndrome (CSS), direct viral invasion through the ACE2 receptor, and RAAS imbalance which are potentially related to this condition.[8,16]

Cytokine storm syndrome (CSS) is associated with AKI

Observational data from a subgroup showed coronavirus infection has a strong connection to triggering cytokine storm syndrome. This is proved by the elevation of inflammatory serum markers such as C-reactive protein, ferritin, erythrocyte sedimentation rate, D-dimer, fibrinogen, and lactate dehydrogenase are predictors of critical illness and mortality in COVID-19 patients. High elevations of the IL-6 cytokine in serum have been associated with fibrinogen levels and poor prognosis in COVID-19 patients.[12]

There were some evidences of increasing levels of inflammatory cytokines in Covid 19 patients. The case report from Huang et al., interleukin-1β (IL-1β), IL-1RA, IL-7, IL-8, IL-9, IL-10, fibroblast growth factor (FGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon -γ (IFN γ), granulocyte colony-stimulating factor (G-CSF), interferon-γ-induce protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), platelet-derived growth factor (PDGF), tumor necrosis factor (TNFα), vascular endothelial growth factor (VEGF) were detected in large amounts of patients infected with COVID-19, especially intensive care patients. Furthermore, cytokines can interact with kidney cells and stimulate endothelial and tubular dysfunction. For example, TNF- alpha can bind directly to tubular cell receptors and then

stimulate apoptosis in cells.[8,16]

T-cell Lymphodepletion can cause over-activation of the Immune system, which leads to the dysregulation of the cytokine-release syndrome. These situations are often found in the severe symptom of COVID-19 patients. Recent studies have demonstrated that rapid viral replication, antagonism of interferon signaling, and neutrophil and monocyte-macrophage activation are mediators of hyperinflammation. Another study showed that the rising of IL-6 also causes an increase in renal vascular permeability. This condition is also aided by the secretion of pro-inflammatory cytokines (IL-6, IL-8, and MCP-1) in renal endothelial cells causing micro circular dysfunction. Therefore, there is a possibility of cytokines involvement in COVID-19 infection with AKI.[12,16]

The histological findings showed polymorphic lesions of the renal tissue, for instance, acute tubular necrosis (ATN), tubulointerstitial nephritis (TIN), glomerular disintegration (with podocytopathy), and thrombotic microangiopathy (TMA). ATN and TIN were often found in septic conditions – hemodynamic changes, coagulopathy, and direct toxic conditions may result from the elevation of cytokines level (IL-6 and TNF) in renal epithelial cells.[8,16] The evidence found to date is still very minimal. The histological findings may occur during severe infections and high levels of virus in the body.[8]

Direct virus invasion

Viruses can enter the host cell by attaching to cell receptors, which can replicate. The cell invasion depends on ACE2 expression and the presence of the protease TMPRSS2 (transmembrane protease, serine 2), which can cleave the viral spike and enter the host cell.[16]

Infection and replication of SARS-CoV-2 in renal tubular cells and podocytes causes ATI and ATN to progress to TIN, which is exacerbated by cytokine storm syndrome (CSS). Meanwhile, fibrin thrombi and TMA patterns in renal cedar can be seen in hypercoagulable conditions. All processes that occur in renal injury in the parenchyma can be described as COVID-19 nephropathy. Another histological biopsy result from SARS-CoV-2 patients with AKI showed glomerulopathies and severe podocyte thinning with acute tubular injury (ATI). The hyperinflammatory state can cause renal injury via multiple mechanisms, as highlighted. However, the discussion is incomplete without further assessing the role of direct viral tropism for renal parenchyma and renal autopsy findings.[8]

Patients with dysregulation or genetic variation of ACE2 can accelerate the infiltration of SARS-CoV-2 and will show early signs of kidney disease with new onset of proteinuria and haematuria. However, there is a need for in-depth studies of renal histology in COVID-19 to explain the mechanism of kidney injury in detail.[8]

Imbalanced RAAS activation

The renin-angiotensin-aldosterone system (RAAS) is a series of regulatory peptides that participate in key physiological processes of the body, including fluid and electrolyte balance, blood pressure regulation, vascular permeability, and tissue growth. While ACE2 acts as a potent counter-regulator of the RAAS pathway. The maladaptive function of the RAAS has an important role in tissue damage by SARS-CoV-2 infection.[12,16] When the SARS-CoV-2 virus attaches to ACE2 and triggers down-regulation of the ACE2-binding membrane, it causes an increase in the accumulation of angiotensin II by decreasing the degradation of angiotensin 1-7. Thus, COVID-19-mediated accumulation of angiotensin II may lead to an imbalance of RAAS activation. This process causes inflammation, fibrosis, and vasoconstriction. Additionally, ACE2 interacts with the angiotensin receptor 1 (AT 1) to form a complex that prevents the internalization and degradation of ACE2 membrane binding to lysosomes. The presence of angiotensin II accumulation decreases the interaction and internalization of ACE2 membrane binding to lysosomes.[16]
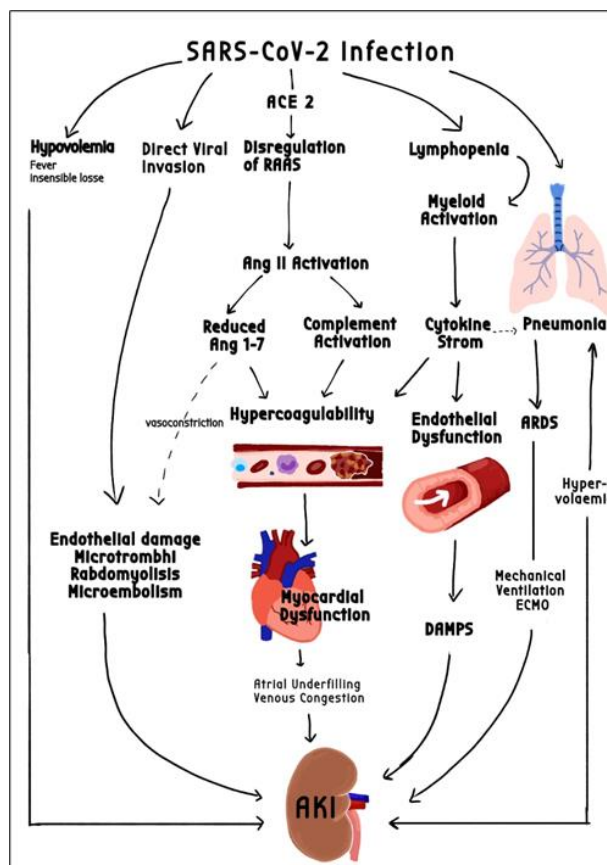
Figure 1. Acute kidney injury in COVID-19

Multiple dependent pathways in the setting of COVID-19 increase the risk of acute kidney

Cross mechanism between lung and kidney

Lung-kidney cross-talk is based on the similarities that both of these organs share, and this interaction is becoming a topic of interest due to the frequency of involvement of both organs by SARS-CoV-2. Respiratory failure can trigger AKI due to multiple etiologies such as 1) systemic hypoxia, 2) hypercapnia, 3) acute lung injury leading to SIRS, and 4) even mechanical ventilation.[17]

The hypoxia can lead to AKI and tubular necrosis or apoptosis. Furthermore, hypercapnia in COVID-19 patients can affect renal vascular circulation by stimulating vasoconstriction. An important point with this cross-lung-kidney mechanism is its association with cytokine storms. The inflammatory reaction causes lung injury that can damage the kidneys to produce inflammatory cytokines. Thus, limiting the use of ventilators and reducing the duration of

mechanical ventilation may contribute to the development of AKI in critically ill COVID-19 patients.[18] The cross-mechanism between lung-kidney in AKI and ARDS has been observed. Mechanical ventilation can improve lung function. However, it also worse the AKI in individuals. The positive pressure of mechanical ventilation can increase the risk of AKI eight times, which is associated with hemodynamics, neurohormonal changes, and barotrauma.[18]

Management of AKI in COVID-19

The supportive guidelines in Covid-19 patients with kidney involvement implement the Kidney Disease: Improving Global Outcomes (KDIGO) (e.g., avoidance of nephrotoxins, regular monitoring of serum creatinine and urine output, consideration of hemodynamic monitoring). The body volume loss can occur in the early therapy due to fever, gastrointestinal

symptoms, or heart failure. Therefore, the volume management should aim to resuscitate, stabilize blood pressure and achieve the arterial volume target.[10] In patients with grade 1 or 2 AKI who are euvolemic, the furosemide stress test can help to identify the risk of developing AKI that is progressive and requires RRT.[19]

Crystalloid fluid is recommended for volume resuscitation because it has a lower incidence of AKI. The SMART trial compares the use of crystalloid solutions with normal saline in 13,347 patients and found that side effects on the kidneys were 4.7% vs. 5.6%. This indicates that crystalloid solutions have fewer side effects than normal saline. Acidosis is an independent risk factor for developing AKI in ARDS. Isotonic bicarbonate can be given to hypovolemic patients with significant metabolic acidosis (pH < 7.20) and AKI. When the volume has been accomplished, the next step is to maintain that level.[8]

Renal replacement therapy (RRT)

If the conservative management fails, RRT will consider as an alternative in patients with volume overload, especially those with refractory hypoxemia. In COVID-19 patients with AKI, early stages of RRT and sequential extracorporeal organ support (ECOS)

are likely to support adequate organ support and prevent disease progression. Indication to perform RRT therapy follows the guidelines for Kidney Disease Improving Global Outcome (KDIGO).[10,19] Indications of patients requiring RRT therapy are oliguria with volume overload, hyperkalemia, severe acidosis, and azotemia. In patients with cytokine storms, the extracorporeal needed to remove cytokines even though AKI is not present.[10] Adequate central venous access is essential for the availability of blood flow during RRT. The length of the hemodialysis catheter (15-16 cm for the right internal jugular, 19-20 cm for the left internal jugular, 24 cm for the femoral) and the location chosen must be selective because the inadequate blood flow increases the clotting. The right internal jugular vein is the preferred access for RRT because it provides a direct path for the catheter tip to be at the desired location – the junction between the superior vena cava and the right atrium.[10,19]

Hypercoagulation often occurs in patients infected with COVID-19 during the RRT process. Thus, citrate anticoagulant should be given because it has better efficacy than other anticoagulants.[10]
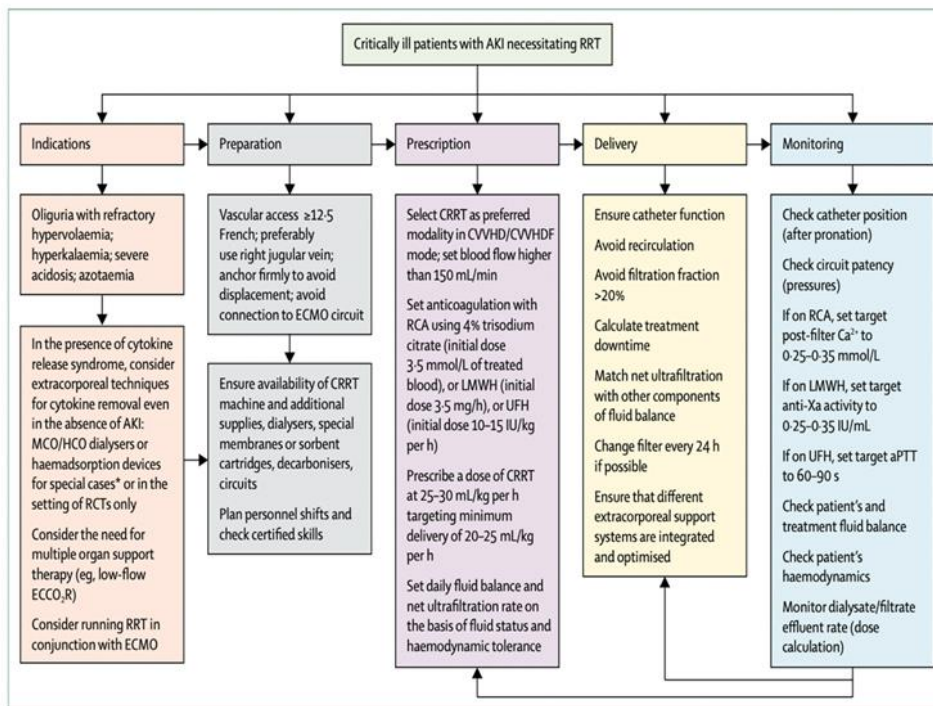

Figure 2. Management of acute kidney injury necessitating renal replacement therapy in patients with COVID-19.[10]

Continuous renal replacement therapy (CRRT) and extracorporeal

CCRT therapy is the recommended modality for the management of AKI in unstable hemodynamic patients.[19] More than 20% of COVID-19 patients require RRT, especially continuous renal replacement therapy (CRRT), due to AKI conditions with electrolyte imbalance and/or fluid overload.[8] CRRT initiation time is different between each center; There are two RCT studies in the last 10 years that showed no significant difference in patients with AKI stage 3 who underwent HD/RRT initiation at 6-12 hours and 48 hours, in mortality, ICU-free days, ventilator-free days and vasopressor-free days. Most patients have improved renal function without CRRT. In COVID-19 patients with ARDS and AKI, several studies have shown that early initiation of CRRT in ARDS improves oxygenation and mechanical ventilation-free days. The technique of delaying the initiation of CRRT is carried out in COVID-19 patients with septic shock, namely for 48–72 hours after becoming AKI Stage 3 or until there is an absolute indication for CRRT. CRRT initiation is an early need in ARDS patients who do not respond to adequate diuretic therapy.[8,10,19]

Intermittent hemodialysis (IHD)

IHD is the conventional modality for performing RRT in hemodynamically stable patients. According to the Acute Renal Failure Trial Network (ATN), KDIGO and the Kidney Disease Outcomes Quality Initiative (KDOQI) recommend IHD three times/week using a single pool Kt/Vurea of 1.3 per session. The modality of IHD in COVID-19 patients may require one-on-one care support, both in the ICU and in the regular ward.[10,19]

On the other hand, this modality increases the exposure of nursing staff, and creative strategies are needed to minimize the exposure and length of time for patient care by reducing the frequency of dialysis and telemonitoring (using monitors/tablets to monitor the patient's condition from outside). Reducing the time and/or frequency of hemodialysis treatments can result in uremia and metabolic disturbances, and

patients should be monitored for manifestations of inadequate dialysis.[19]

Hypercoagulability and RRT

The hypercoagulable phase may lead to an increased risk of thrombotic complications in patients with confirmed COVID-19. In addition to deep vein thrombosis and pulmonary embolism, clotting of extracorporeal circuits is a serious concern because it can cause significant blood loss and excessive loss of the RRT filter. The study from Sana S et al. recommends that every patient with COVID-19 who initiates CRRT or PIRRT therapy receive anticoagulation according to the protocol listed.[19]

If the initial anticoagulation strategy is ineffective, then an alternative plan is needed. At the Sana et al. study center, systemic unfractionated heparin was administered to all COVID-19 patients on CRRT (target-activated partial thromboplastin time is 60-90 seconds). If the patient develops bleeding or others complication from unfractionated heparin, the use of regional citrate anticoagulation (RCA) is an alternative option. While in some centers, RCA is becoming the first-line anticoagulant for CRRT. The implementation of this RCA is difficult and requires intensive care techniques, so it is not recommended to use a hasty RCA protocol because it can cause dangerous side effects. In another research center, the anticoagulant methods used for CRRT are low-molecular-weight heparin (LMWH) and direct thrombin inhibitors. Therefore, the involvement of a pharmacologist (pharmacist) to determine the adequate dosing and prevent errors.[19]

Management of COVID-19 in kidney recipients

Renal transplant recipients with COVID-19 have a higher incidence of AKI and mortality compared to the general population. Data from the cases series showed the proportion of COVID-19 patients who develop AKI with a history of renal transplant was 30%-57%, and the mortality rate of up to 28%.[8]

Individuals commonly experience gastrointestinal symptoms, particularly diarrhea that causes

hypoperfusion of the renal parenchyma and loss of bicarbonate ions. Therefore, fluid resuscitation in the early phase, stabilizing blood pressure, and avoiding the use of nephrotoxic drugs, including ACE inhibitors and ARBs, should be noted. Viral infections can be severe in patients on immunosuppressant therapy because of T cell-mediated immune response. Transplant recipients infected with COVID-19 should receive an immediate immunosuppressant adjustment based on the severity of the illness.[8]

Generally, anti-metabolites (mycophenolate mofetil and azathioprine) should stop. The dose of Calcineurin Inhibitor (CNI); tacrolimus, cyclosporin) should be reduced by 50% or stopped completely in severe cases. Thus, the target dose of tacrolimus is 3–5 ng/mL, and cyclosporine is 25–50 ng/mL. The mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus) should be stopped or replaced with CNI. The mTOR inhibitors may worsen COVID-19 pneumonia because of the side effect of pneumonitis. During the initial phase, the steroid therapy should change to the stress dose strength.[8]

The time frame to restart immunosuppressant therapy is unclear and can be considered if clinical conditions improve and the SARS-CoV-2 PCR swab result is negative. Therefore, a multidisciplinary approach is needed to evaluate the risks and benefits of restarting immunosuppressive therapy. CNI therapy was started at half the maintenance dose and increased titration over two weeks. Steroids are administered at a stress dose throughout the titration period. Anti-metabolites and mTOR inhibitors are recommended after 2-4 weeks, depending on the course of the case. Drug interactions should be considered in transplant recipients because rejection may occur if the immunosuppressant is stopped.[8]

2. Conclusion

The manifestation of acute kidney injury (AKI) in COVID-19 patients is a challenge for nephrology to establish the basis for diagnosis and therapy. In COVID-19 patients, kidney disorders have proteinuria and hematuria signs at the beginning of treatment.

Individual age and comorbidities increase the risk of AKI. Management of COVID-19 patients with AKI is generally the same as other etiologies such as sepsis. The conservative management of volume overload, metabolic acidosis, and hyperkalemia can be performed before further management, namely RRT. Patients with COVID-19 are at high risk of circuit clotting during CRRT and PIRRT. Therefore initiation of anticoagulation should be performed when initiating RRT.

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