Narrative Review

COVID-19 in Renal Transplant Patients – A Narrative Review

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Abstract

The World Health Organisation declared the novel coronavirus known as severe acute respiratory syndrome coronavirus 2 a pandemic in March 2020. This virus has led to the deaths of more than 6 million people worldwide. Besides causing pneumonia, COVID-19 is linked to multiple organ dysfunction, including the kidneys, especially in individuals whose immune systems are already compromised. Consequently, individuals who are currently on a waiting list for a kidney transplant or who have recently received a kidney transplant are at a significantly increased risk for developing acute kidney injury and are severely impacted by the COVID-19 infection. The pandemic has negatively affected the transplantation process and led to a decrease in the number of organ donations as well as the volume of renal transplants. This review summarises the outcomes of COVID-19 infection in renal transplant patients, its pathophysiology, the challenges faced by the transplant community, and the management of immunosuppression.

Keywords: Acute kidney injury, COVID-19, kidney transplant recipients, renal transplantation, severe acute respiratory syndrome coronavirus 2

Introduction

Numerous cases of pneumonia were reported in the city of Wuhan, China, and COVID-19 was later identified as the cause.[1] While 60%–70% of the patients remain asymptomatic, the remaining cases can present with fever with cough, fatigue, dyspnea, and malaise.[2] The spike proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) bind to angiotensin-converting enzyme 2 (ACE2) receptors and enter the cells of the respiratory system and other organ systems due to the widespread presence of ACE2 receptors, including the kidneys.[3] The average incubation period is five to six days which can vary, primarily due to age and the intensity of the immune response.[4] When compared to the young population, those aged 60 or older are likely to contract the SARS-CoV-2 infection and, once infected, have a more severe course of the illness.[5] Respiratory failure is a common cause of mortality in COVID-19 patients, followed by sepsis, heart failure, and kidney failure. The virus can trigger a systemic inflammatory syndrome which may become severe and cause a multiorgan failure.[6] In the lungs, it causes interstitial pneumonia, which is characterised by inflammation, infiltration, and rupture of the alveoli. In addition, the reduced gas exchange causes wheezing and coughing.[7] A sharp rise in the inflammatory response may harm the heart and blood vessels, raising the likelihood of vasculitis and myocarditis. In severe cases, there are even examples of fatal cardiac arrhythmias and myocardial infarction. Excessive inflammatory responses would set off a chain of events that would result in blood clotting, increasing the risk of intravascular clots and pulmonary embolisms.[8] It causes strokes and inflammation of the brain, which can lead to confusion and seizures.[9] Due to the cytokine storm and the SARS-CoV2 infection, the patient has acute kidney damage (AKI) in the renal system, which ultimately leads to renal failure.[10]

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The renal involvement in COVID-19 infection is a well-known fact, and higher mortality (97.1% vs. 8.8%) is seen in COVID-19-infected patients with either a preexisting renal disease or new-onset AKI compared to those without any evidence of renal injury.[11] The COVID-19 infection presents a risk to the patients awaiting renal transplant and after completion.[3] The incidence of developing AKI is also greater in renal transplant patients than in the nontransplant patient population. Around 54% of renal transplant patients suffering from COVID-19 developed AKI compared to 25% of nonrenal transplant patients.[12] Transplant patients with COVID-19 infection are also more likely to have a severe disease course than the general population. The study showed an increased requirement for renal replacement therapy (15.4% vs. 3.3%) and a longer intensive care unit stay (34.1% vs. 13.3%) in renal transplant patients when compared to nontransplant patients.[13] The attributable mortality due to the COVID-19 disease in renal transplant recipients was almost 20% more than the mortality in transplant patients without the viral infection.[14] According to the French National Registry data, 44% of renal transplantation patients and 42% of the transplant candidates died from COVID-19 infection from March 1, 2020, to June 1, 2020. Most deaths occur during the first 12 months posttransplantation when the immunosuppression is at its maximum. The evidence of increased mortality due to COVID-19 in these groups was further consolidated as increased deaths were reported from March 2020 to June 2020 compared to the previous two years. Between these two groups, more deaths were seen in the patients waiting for the transplant than in the patients who already got transplants.[15] The nonsurvivor renal transplant patients are more often older adults with a low baseline lymphocyte count, glomerular filtration rate (GFR), and serum creatinine levels than transplant patients who survived the COVID-19 infection.[16] The immunosuppressed state of these patient populations plays a vital role in escalating this risk. In addition, multiple preexisting comorbidities such as hypertension, diabetes, history of smoking, heart disease, and obesity are common in renal transplant patients, increasing the risk of hospitalisation and mortality in these patients.[17] Managing the immunosuppression in COVID-19-positive renal transplant patients is challenging and may differ for each patient. Age, preexisting comorbidities, the severity of infection, and time since the transplant may play a role in deciding the treatment.[18]

Another way the pandemic has impacted renal transplantation is by suspending various transplant programs. A survey suggested that around 72% of live kidney donor transplant programs saw either a complete or partial closure.[19] The consensus around utilising the kidney of a potential donor infected with COVID-19 is also an issue. The risk of transmission of the virus to the transplant recipient through blood and exposing the transplant team to the infection is a few negative consequences to consider.[20] We have reviewed literature from PubMed using different keywords to understand the pathophysiology, diagnosis, and management of renal transplant patients suffering from COVID-19 infection.

Pathophysiology

COVID-19 is considered a respiratory illness; however, the kidney is also a target of an infection caused by SARS-CoV-2. This is because of the ACE2 receptors which allow the virus to enter the cells, which are found in abundance in the kidney.[21] In the kidneys, expression of ACE2 is mostly in the apical brush borders of the proximal tubules, and to less intensity in the podocytes.[22] COVID-19 causes AKI in 30%–89% of hospitalised kidney transplant recipients,[17] with a graft loss of approximately 11%, according to a report from the New York City Transplant Centre.[23] SARS-CoV-2 induces AKI in COVID-19 patients through several prerenal and renal pathophysiologic mechanisms. The renal mechanism of AKI includes direct impact on the kidneys, immune response kidney injury,[24] and coagulopathy leading to microvascular dysfunction secondary to endothelial damage.[25] When the spike (S) protein binds to the ACE2 receptor and is primed by proteases from the TMPRSS family, the viral protein is able to penetrate the host cell and directly influence the kidney. On histopathological examination of the infected kidneys, clusters of coronavirus particles can be seen with distinctive spikes in tubular epithelial cells and podocytes.[24] In addition, the immune response induces CD68+ macrophage infiltration into the tubulointerstitium and enhances complement C5b-9 deposition in the tubules.[17]

Acute tubular necrosis (ATN) is also seen with COVID-19, which results in the loss of brush border epithelium. The causes of ATN include severe inflammation, direct viral infection, and hypovolemia.[26] There are also several prerenal mechanisms of AKI in COVID-19 that are also common in kidney transplant recipients, including cardiorenal syndrome, acute lung injury, and drug-induced nephrotoxicity. COVID-19 is known to cause viral myocarditis, which leads to ventricular dysfunction and decreased perfusion to the kidney, which can lead to AKI. Acute lung injury, by causing decreased medullary perfusion due to hypoxemia, can also lead to AKI. Use of immunosuppressants, especially calcineurin inhibitors (CNI) which are the mainstay of management of immunosuppression in kidney transplant recipients, and other antivirals against COVID-19 are nephrotoxic and can lead to AKI, which makes it difficult to distinguish nephrotoxicity from chronic allograft rejection.[21,27]

Treatment of KTR with COVID-19, apart from frequent hand washing, face masks, and social distancing, includes decreasing the dose of immunosuppressive drugs and, in some cases, using antivirals against COVID-19. The general consensus regarding the use of immunosuppressive drugs in KTR is the withdrawal of antimetabolites in most patients and the withdrawal of CNI and/or mammalian target of rapamycin inhibitor (mTORi) in a smaller number of patients with the addition of steroids. Corticosteroids

are commonly used for immunomodulation to prevent and treat graft rejection in kidney transplant recipients.[28] Management of immunosuppression based on the severity of COVID-19 involvement in kidney transplant recipients, who are beyond three to six months after transplantation has been provided by European Renal Association-European Dialysis and Transplantation Association and Developing Education Science and Care for Renal Transplantation in the European States working group.[29] In KTRs who are on immunosuppressant drugs, including CNI and mTORi, use of antiviral drugs such as ritonavir or cobicistat should be used cautiously, with dose reduction or complete withdrawal of these immunosuppressants. In a randomised control, the use of these antiviral drugs did not show any clear benefit due to the high risk of drug-drug interactions and the trial concluded against their routine use in KTRs.[29]

The use of azithromycin and hydroxychloroquine which were frequently used in earlier months of the pandemic, has now been stopped, as studies show no benefit in their use and some instances indicate harm.[30] The use of remdesivir in transplant patients is not clearly addressed, as the studies excluded patients with severe AKI, chronic kidney disease with an estimated GFR of 30 ml/min/1.73. Therefore, at this time, additional tests are needed to determine whether or not remdesivir is safe and beneficial for this population. Despite this, many hospitals in the United States continue to use it for transplant patients who are hospitalised and have COVID-19 pneumonia.[28]

Conclusions

Patients who have undergone renal transplantation have been significantly impacted by this virus. Patients who have undergone kidney transplants are more likely to have COVID-19 infection due to the immunosuppressive medications they take. This is because their bodies are rendered virtually defenseless against the SARS-CoV-2 infection. As a result, COVID-19 has a significant impact on waitlisted patients, reducing their chances of receiving a kidney transplant and posing a significant risk of death. The COVID-19 disease has also been linked to patients developing a new kidney injury or experiencing a worsening of their AKI symptoms. To enable kidney transplantation, centres should implement COVID-19 protocols, both by improving hospital safety and by implementing patient communication systems. Although majority of people consider SARS-CoV-2 to be an illness of the respiratory system, the kidney can sometimes be affected just as much, if not more, than the respiratory system. SARS-CoV-2 has affected millions worldwide and has the potential to have fatal consequences for all people. However, the findings of this article suggest that patients who have renal failure or who have received a kidney transplant may be affected more severely by SARS-CoV-2 than normal people. As a result, patients should be educated by their doctors on how to avoid becoming infected with SARS-CoV-2 and encouraged to receive the COVID-19 vaccination. Fortunately, the COVID-19 pandemic is resolving in some countries and China, thanks to vaccination and lockdown and the subsequent widespread use of effective COVID-19 vaccines. The recent outbreak of a variety of SARS-CoV-2 variants has created a new challenge for scientists to develop the most effective COVID-19 vaccine.

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Conflicts of interest

There are no conflicts of interest.

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