Review Article

Kidney Allograft Rejection and Coronavirus Disease 2019 Infection: A Narrative Review

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Abstract

The world has experienced a global medical and socioeconomic burden following the coronavirus disease 2019 (COVID-19) pandemic. COVID-19 is a systemic disease and may affect different organs including the kidneys. Current literature contains reports on COVID-19-related conditions such as acute kidney injury, and complications experienced by chronic kidney disease, end stage kidney disease, and kidney transplant patients. Here, we discuss the incidence of kidney allograft rejection, immunosuppression management and rejection risk, donor-specific antibodies and previous rejection episodes, and rejection outcomes in kidney transplant recipients with COVID-19 by reviewing current studies.

Keywords: Coronavirus, immunosuppression, kidney transplantation, rejection

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Introduction

Coronavirus disease 2019 (COVID-19) is as a viral infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] It spread very quickly around the world, causing global medical and socioeconomic burden following its pandemic.[1] COVID-19 is a systemic disease and may affect different organs including the kidneys.[2,3] Current literature contains reports on COVID-19-related conditions such as acute kidney injury, and complications experienced by chronic kidney disease, end stage kidney disease, and kidney transplant patients.[2] Among the different mechanisms proposed for the pathogenesis of COVID-19 renal involvement, acute tubular injury as well as lymphocytic infiltration of kidney tissue are most common.[2] The other suggested mechanisms are kidney involvement through direct viral infection, indirect injury by sepsis, hemodynamic alterations, cytokine storm, disseminated intravascular coagulation, proximal tubule dysfunction, hypercoagulability and terminal complement activation causing micro-angiopathic injuries, rhabdomyolysis, and collapsing glomerulopathy during COVID-19 infection.[2,3]

Current studies showed that the common presentations of COVID-19 among kidney transplant recipients (KTRs) are cough, dyspnea, and gastrointestinal symptoms. However, fever is the most common presentation in these patients.[4] The patient's age—ranging from 45 to 61 years—as well as the gender ratio were variable in different studies.[2] The time interval between kidney transplantation and onset of COVID-19 presentation was also variable,[2] such as a median interval of 2 years reported by Banerjee *et al*.[5] and about 13 years reported by Alberici *et al*.[6] Like the variable demographics across the studies, adjustments in baseline immunosuppression and COVID-19 management vary widely in different studies.[2] There are some *in vitro* evidences for efficacy of calcineurin inhibitors (CNI) to diminish the viral growth.[7,8] Mortality rate varies between 7% in a survey performed in United States and

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32% as reported in previous studies.[2] Akalin *et al*. reported a need for mechanical ventilation in 39% of their COVID-19 KTRs while rate of mechanical ventilation in Alberici *et al*.'s study was zero.[4,6,9] The need for renal replacement in COVID-19-infected KTRs was as low as 5% in the study by Alberici *et al*.[6] High rate (43%) of renal replacement therapy had been reported by Banerjee *et al*.[5] Therefore, given the importance of the issue, this paper reviews studies on kidney allograft rejection and COVID-19.

Incidence of Allograft Rejection

According to the literature, incidence of kidney allograft loss due to COVID-19 infection was variable but less than 10% in the articles published so far. The most common renal event in the kidney transplant recipients following COVID-19 infection was acute kidney injury (AKI) ranging from 30% to 57% in different studies.[2] In a cohort study on 79 in-patient, COVID-19-infected KTRs, 23% of patients developed AKI following infection and required dialysis during the course of the disease; among them five patients remained dialysis-dependent and lost their kidney allograft.[10] In another study conducted by Craig-Schapiro *et al*.[11] on 47 KTRs admitted with COVID-19 infection, four out of 25 patients who developed AKI became dialysis-dependent during admission and lost their allograft. AKI was reported to develop in 48.4% of cases in a cohort of 250 kidney transplant recipients infected with COVID-19. It was more common among severe and moderate cases of COVID-19 than mild and asymptomatic cases.[12] Twenty-four patients (9.6%) underwent dialysis during admission, of whom 12 remained dialysis-dependent. Authors reported that 77 patients had allograft dysfunction before becoming infected with COVID-19.[12] The largest study was conducted by Caillard *et al*.[13] in which 43.6% developed AKI, 11.1% underwent renal replacement therapy (RRT), and 9 patients (3.2%) lost their kidney allografts in their cohort of 279 KTRs infected by SARS-CoV-2. None of the aforementioned articles did kidney allograft biopsy; thus the mechanisms responsible for allograft loss was not reported.

Incidence of allograft rejection following infection with SARS-CoV-2 in KTRs is highly variable among individual studies, ranging from none to 27%.[14–23] This variability in incidence of allograft rejection could be, on one hand, due to the short follow-up intervals in some studies and, on the other hand, the absence of allograft biopsy findings in a bunch of other studies indicating that some subclinical allograft rejections may have gone unreported.

Chen *et al*.[14] followed 30 COVID-19-infected KTRs for 14 days after testing positive for COVID-19 polymerase chain reaction (PCR) test; although 77% of patients developed AKI during the course of disease, allograft rejection was not reported in any of them. Elec *et al*.[15] followed up with 42 KTRs infected with COVID-19 for a longer interval—more than one month after a SARS-CoV-2-positive PCR test—however they also did not report any case of allograft rejection. Serum positivity for anti-SARS-CoV-2 IgG was not associated with the risk of kidney transplant rejection, according to a study by Asti *et al*.[16] They screened a cohort of 201 kidney transplant recipients for SARS-CoV-2 IgG antibody; among those who experienced kidney transplant rejection, only two patients were positive for SARS-CoV-2 antibody.

Another cohort of 47 kidney allograft recipients who were hospitalized with COVID-19 did not report any case of kidney allograft rejection in a follow-up of three months, although four patients had known donor-specific antibodies (DSA) titers. Similar to the previous study, the most common approach regarding immunosuppression reduction was withdrawal of antimetabolites.[17] Unlike the above-mentioned articles, there are studies that found an association between COVID-19 and allograft rejection, raising concern about the correlation between immunosuppression management during COVID-19 infection and higher risk of allograft rejection and also the immune dysregulation caused by COVID-19 infection and its role in triggering donor specific antibodies.[24] In a study by Kates *et al*.,[18] 318 patients were followed for 28 days after positive PCR test, among whom seven cases of acute kidney allograft rejection were reported that included six cases of acute cellular rejection and only one case of acute antibody-mediated rejection (AMR).[18] However Pascual *et al*.[19] reported a rejection rate of 8% in a cohort of 24 KTRs who were hospitalized for COVID-19. Their immunosuppression management was antimetabolites and CNIs holding in 96% and 62.5% of patients, respectively. Chavarot *et al*.[20] reported two cases of acute kidney rejection in a cohort of 100 KTRs hospitalized due to COVID-19 over a median follow-up of 13 days; authors did not specify the rejection mechanism. These studies did not report data regarding allograft biopsy, including how many individuals underwent biopsy and why the biopsy was indicated. Thus, they do not provide a reliable incidence of rejection in COVID-infected KTRs.

By contrast, a rejection rate of 27% was reported in 18 patients who underwent allograft biopsy due to AKI less than one month after SARS-CoV-2 PCR positivity. Authors concluded that the risk of kidney allograft rejection was significantly higher in COVID-19-infected patients than non-COVID KTRs.[21] In another case series of COVID-19 patients who underwent kidney biopsy due to renal impairments, two of the three patients with kidney allografts developed AMR.[22] In a cohort of 42 KTRs who developed AKI following hospitalization for COVID-19 infection, the patients were followed for a median of 5.23 months. Eleven patients underwent allograft biopsy that revealed four (9.5%) cases of graft rejection.[23]

COVID-19 Infection Characteristics and Allograft Rejection

We did not find a significant correlation between COVID-19 severity and the risk of allograft rejection, but most of patients who experienced allograft rejection following COVID-19 infection had a severe course of the disease.[7–9,25] Of note,

the rejection was also reported in asymptomatic and mild cases.[9] Hence, although allograft rejection is more prevalent in severely infected patients, it should also be considered in mild cases.

In all but two studies, rejection was documented at least one month after positive SARS-CoV-2 PCR test.[4,5,7,9,25,26] Those include the study conducted by Chavarot *et al*., which reported two cases of rejection in a follow-up period of 13 days after positive COVID-19 test, and other cases of allograft rejection in 15 days after COVID-19 symptom unset as reported by Alberici *et al*.[6,8,9,20,27]

Immunosuppression Management and Rejection Risk

Whether or not immunosuppression reduction in KTRs following infection results in increased risk of rejection remains a controversy. Posadas Salas *et al*.[28] concluded that any reduction in immunosuppression including tacrolimus trough level <8 ng/ml and/or mycofenolate mofetil dose <1000 mg/d, sustained for at least a month within the first year after transplantation following a bacterial, viral, or fungal infection, increases the risk of allograft rejection. Their cohort consisted of 178 KTRs infected with any of the aforementioned agents. The donor's race, comorbidities of the participants, marginal donor characteristics, delayed graft function, and cytolytic induction therapy were amongst the proposed associated factors with immunosuppression reduction.[28] In contrast to this, immunosuppressant dose reduction did not cause any allograft rejection in a follow-up period of two years following bacterial pneumonia in 16 patients; the immunosuppressive protocol in this study consisted of glucocorticoids, cyclosporine, tacrolimus, mycophenolate mofetil, and sirolimus in various combinations.[29] Likewise in 20 KTRs who developed bacterial pneumonia and underwent immunosuppressant dose reduction, no case of allograft rejection was reported two years afterward; the immunosuppressant regimens consisted of oral corticosteroids, tacrolimus, cyclosporine, mycophenolate mofetil, and sirolimus.[30] This variability in results could be attributed to the small sample size of the latter studies.

Immunosuppression reduction outcomes in COVID-19 KTRs are also variable. Chen *et al*.[14] concluded that immunosuppression reduction does not increase the risk of allograft rejection. They followed up on a cohort of 30 patients for 14 days. Their immunosuppression regimen consisted of withdrawal of antimetabolites and CNI while continuing administration of low dose prednisone (5 mg daily); 60% of patients also received a high dose of methylprednisolone (40–455 mg). Another cohort of 42 SARS-CoV-2 PCR-positive patients with the same strategy toward the immunosuppression management did not report any case of allograft rejection up to one month after discharge.[15] Authors suggested that COVID-19-induced lymphocytopenia may allow for the aggressive immunosuppression reduction so-called drug holiday period. Immunosuppression reduction consisted of holding the antimetabolite (mycophenolate mofetil or mycophenolic acid) with or without adjustment of CNI. Tacrolimus was withdrawn in patients receiving antiretrovirals and adjusted to maintain a trough level of 4–6 ng/ml in the other patients. Steroids were either converted to intravenous for stress dosing or kept at the maintenance dose.[15] On other side of the coin, following the withholding of antimetabolites and CNIs in a cohort of 42 COVID-19-infected KTRs who developed AKI in the course of infection, four patients developed allograft rejection in a median follow-up period of 5.23 months. Authors concluded that the risk of allograft rejection could be attributed to the immunosuppressant reduction strategy.[23] Lower incidence of allograft rejection in the first two studies discussed here could be due to the lower follow-up period of these studies.

Rejection has been documented in KTRs infected with COVID-19 without any change in their immunosuppression management, which suggests that the infection itself—and not the reduction in immunosuppressants—may lead to allograft rejection. In a cohort of 18 KTRs who underwent kidney allograft biopsy less than one month after COVID-19 infection, five cases of allograft rejection were detected. Immunosuppressive drugs were unaltered until biopsy findings were released.[21]

It has been reported in several studies that most of the KTRs on presentation were on maintenance immunosuppression comprising of tacrolimus, mycophenolate mofetil, and prednisone.[2,31]

Donor Specific Antibodies and Previous Rejection Episodes

Newly elevated titers of DSA have been associated with increased risk of late acute AMR, chronic AMR, and transplant glomerulopathy.[32]

In a study by Bajpai *et al*.,[23] one patient (2.4%) developed *de novo* DSA in the course of COVID-19 infection. In contrast to this, none of the 47 KTRs who had COVID-19 in the cohort of Pampols *et al*.[17] developed *de novo* DSA up to three months after infection.

Having a history of allograft rejection was associated with poor renal outcomes in the reviewed studies. According to a report by Bajpai *et al*.,[23] out of 12 patients who had experienced kidney allograft rejection in the past, 11 did not recover allograft function following renal failure due to COVID-19 infection. Having a history of allograft rejection prior to COVID-19 infection or having already elevated titers of DSA seems to be common in those who experienced kidney allograft rejection following COVID-19 infection. Daniel *et al*.[21] reported five cases of acute kidney allograft rejection less than one month after infection was detected. DSA had been detected in three patients prior to COVID-19 infection, among whom two also had a history of allograft rejection. The other two from five cases, did not have detectable DSA titers before until allograft

biopsy following COVID-19 infection nor had they any history of allograft rejection.[21] One of the two allograft rejection cases in a study of Akilesh *et al*.[22] also had a history of allograft rejection before being infected with COVID-19. Both cases had developed *de novo* DSA at the time of biopsy. Abuzeineha *et al*.[33] reported a case of AMR following COVID-19 infection who was positive for DSA before infection but had no previous rejection episodes. Therefore, current studies show that those with already elevated titers of DSA or a history of allograft rejection should be considered as a high-risk group for rejection following COVID-19 infection.

Rejection Outcomes

In the study by Daniel *et al*.,[21] two patients lost their kidney allograft function following a COVID-19-induced rejection episode: one of them had a history of graft rejection and was positive for DSA before COVID-19 infection. While the allograft function improved in the follow-up period of several patients (mean: 282 days, median: 363 days), it never reached baseline level (i.e., before COVID-19 infection).[21] Akilesh *et al*.[22] reported two cases of allograft rejection. Plasma exchange plus intravenous immunoglobulin (IVIG) and IV prednisolone followed by rituximab was administered for the first patient; data regarding clinical outcomes was not available.[22] Mycophenolate mofetil (MMF) was held, rituximab dose was reduced, and low-dose prednisone (10 mg/d) was started for the second patient. His serum creatinine improved following treatment but it did not reach baseline level.[22] The AMR case in a study by Abuzeinah *et al*.[33] was treated with IVIG and MMF was re-administered for his rejection episode; his serum creatinine returned to baseline levels following treatment.

Clinical and subclinical AMR has been associated with increased allograft failure in the long-term (five years after biopsy findings revealed AMR).[34] Thus, allograft rejection following COVID-19 poses a risk of allograft failure in years to come.

Allograft biopsy revealed chronic AMR 93 days after hospital admission for COVID-19, as reported by Abuzeineh *et al*.[33] The patient had a severe COVID infection and was discharged after 16 days. During hospitalization, his serum creatinine (Cr) increased from baseline (1.4 mg/dl) to 3.4 mg/dl following two days of admission but started to improve from day 4 and returned to baseline on day 12 of admission. The patient was positive for DSA prior to admission but had no previous rejection episodes. The patient was checked for newly elevated titer of DSA on day 14 which came to be positive at a cytotoxic level, but it was decided to avoid allograft biopsy due to improvement of serum Cr.[33] Finally the patient was discharged with serum Cr of 1.9 mg/dl. Donor-derived cell-free DNA (dd-cfDNA) was checked for the patient at the time of hospital discharge and was reported to be 4.3%. More than two months after discharge, serum Cr started to rise with a dd-cfDNA of 3.5% and presence of DSA. Accordingly, the patient underwent an allograft biopsy.[33] Antimetabolite dose was halved on the early days of infection and then withheld. It is of note that the patient had forgotten his immunosuppressants for two days before hospital admission which further predisposed him to rejection.[33]

Chowdary *et al*.[35] reported a case of suspected T cell–mediated rejection (TCMR) in a new KTR 14 days after she was diagnosed with COVID-19 and 22 days after transplantation. The patient had a severe course of COVID-19 infection. During the hospital admission, tacrolimus and mycophenolate sodium were discontinued for 13 days. On day 13, the patient developed AKI with her serum Cr rising from 1.5 (a week earlier) to 3.25 mg/dl. The allograft biopsy, which was done a day after, was consistent with TCMR. DSA was negative at the time of biopsy. The patient was managed with pulse steroid for her rejection, and tacrolimus and mycophenolate sodium were started again. Allograft kidney regained its function as the patient's serum Cr returned to baseline four months after discharge.

COVID-19 Vaccine Efficacy

The administration of two doses of Sinopharm® COVID-19 vaccine, based on the classic inactivated virus, with an interval of about 28 days to 90 patients on maintenance in-center hemodialysis showed that the rate of seroconversion was 31.1% after two doses of vaccine. Furthermore, the rate of seroconversion was higher in those with a history of COVID-19 than in those without a history of COVID-19.[36] Studies show that both BNT162b2 and mRNA-1273 vaccines induce robust titers of anti-spike IgGs that confer >94% protection against severe COVID-19 in the general population. But many independent studies have reported that only 4%–48% of KTRs have detectable anti-spike IgGs after receiving two vaccine doses.[37] Also, severe cases of COVID-19 still occur in vaccinated transplant recipients, demonstrating their insufficient protection by the current COVID-19 vaccination approach.[37,38] It has been proposed that in KTRs without history of SARS-CoV-2 infection, the likelihood of generating anti-spike IgGs increases if vaccination is performed late after transplantation, may be due to lower levels of immunosuppression. The other factors proposed for increasing this likelihood are having high glomerular filtration rate, and detectable circulating anti-spike IgGs after the first dose of vaccine.[37] Conversely, a lower vaccination response rate had been shown in association with old age, diabetes, high levels of maintenance immunosuppression, patients treated with belatacept (a T cell co-stimulation blocker) or rituximab (used for B cell depletion).[37]

In transplant recipients, maintenance immunosuppression regimens commonly used for the prevention of graft rejection include a CNI and an antimetabolite such as MMF, which may lead to suboptimal response to COVID-19 mRNA vaccines by interfering with T-cell activation along with blocking the proliferation of activated T and B cells and

blocking the proliferation of follicular helper CD4 + T cells, respectively.[37,39]

Approaches proposed to improve COVID-19 vaccine efficacy are mentioned below and need further investigation: modulation of immunosuppression by temporary dose reduction, suspension of MMF, or replacement of belatacept, increasing vaccine immunogenicity, the use of adjuvants, intradermal injection and high antigen doses, administration of a third dose of COVID-19 mRNA vaccine, and passive transfer of anti-SARS-CoV-2 monoclonal antibodies.[37,39,40]

Discussion

The mechanism of post-COVID-19 kidney allograft rejection may be related to the time interval between COVID-19 infection and the development of acute AMR. The COVID-19 infection and its subsequent immunologic derangements per se can trigger the rejection or maybe the withdrawal and dose reduction of immunosuppressive agents are mediating rejection.

Abuzeineh *et al*.[33] reported a patient with severe COVID-19 infection with pulmonary involvement and hypoxia who developed AMR of the kidney allograft and COVID-19 infection simultaneously. The baseline graft function prior to infection was stable (serum creatinine 1.4–1.6 mg/dl). He was on tacrolimus, mycophenolate, and prednisone. Following conservative management of his initial COVID-19 symptoms, he missed his immunosuppressive medications for two days. Subsequently, he had a history of bilateral pulmonary involvement, elevated inflammatory markers, raised creatinine (2.8 mg/dl), proteinuria, and hematuria at the time of hospital admission, and he received tocilizumab during hospitalization. His mycophenolate was discontinued. He had a hydronephrosis and elevated tacrolimus level, resulting in further rising of his serum creatinine. Following resolution of COVID-19 symptoms, urinary catheterization, and dose adjustment of tacrolimus, the serum Cr improved at discharge. However, preexisting DSAs to HLA-DR7 and -DR53 were elevated and some new DSAs to HLA-DQA2 and -DQB2 developed, resulting in a positive cytotoxicity crossmatch. On day 73 post discharge, his COVID-19 PCR was persistently positive and plasma donor-derived cell-free DNA (dd-cfDNA) was elevated. The graft biopsy showed features of chronic active AMR. Following treatment by intravenous immunoglobulin and re-institution of mycophenolate, the graft function improved.[33]

Anandh *et al*.[41] reported a 56 year old male living-donor kidney recipient who developed worsened graft function simultaneously with COVID-19 symptoms. His baseline creatinine was 1.2 mg/dl and increased to 5.2 mg/dl following conservative management of the initial symptoms. The graft biopsy was compatible with chronic active AMR. In addition to this, acute tubular injury with extensive oxalate crystal deposition was found which was attributed to high-dose intravenous vitamin C that was received during management of COVID-19. During his course of COVID-19, the baseline mycophenolate had been discontinued and tacrolimus dose had been halved, which can be responsible for the AMR. However, the timeline showed that the raised creatinine had been found at admission which was prior to immunosuppression withdrawal.[41] As an interesting finding, the electron microscopy of graft biopsy revealed spherical, spiked particles and tubulo-reticular inclusions in the glomerular capillary endothelial cytoplasm.[41] The timeline of the graft dysfunction and the findings of electron microscopy can suggest direct pathogenesis by SARS-CoV-2 through active graft infection.

COVID-19 may be associated with diverse, aberrant, innate, and adaptive immune response underlying various organ involvement and probably the graft rejection. As a feature of dysregulated immune response, elevated blood levels of interleukin (IL)-6, IL-10, tumor necrosis factor (TNF)-α, IL-2R, and IL-8 were found in severe COVID-19 patients.[42–44] Furthermore, the T cell subsets change during COVID-19. For example, decreased numbers of $CD4^+$ T cells and regulatory T cells (Tregs), and impaired differentiation of naive T cells to memory and effector counterparts had been reported.[42–47] IL-6 is the key mediator that can link COVID-19 and the graft rejection. Now, it is well-known that elevated levels of IL-6 play a significant role in the pathogenesis of COVID-19, and anti-IL-6 therapy such as tocilizumab is frequently used to treat patients with the severe disease.[43,48,49] On the other hand, upregulation of IL-6 has been found in kidney and heart graft rejection through perpetuation of inflammatory responses within the grafts and resultant vasculopathy.[50] Additionally, the excessive levels of IL-6 can result in activation of proinflammatory T-helper 17 cell, inhibition of anti-inflammatory Treg, and production of high-affinity IgG antibodies.[51] In fact, following viral infections conditions such as COVID-19 , expression of HLA molecules could be accelerated.[24] Accordingly, vigorous treatment of inflammatory conditions is highly recommended in KTRs.

Conclusion

In the setting of COVID-19 infection, hyperinflammatory states as well as direct cytopathic effects of severe infection may predispose one to kidney allograft rejection. Although re-institution of full-dose immunosuppression as soon as possible is recommended, the correct decision regarding the regulation and administration of immunosuppressive drugs in these patients is controversial and unclear. Future studies should be conducted to clarify the efficacy of various antiviral agents against development of graft rejection, the relationship between severity of COVID-19 and the incidence of rejection, and the timing of graft biopsy. Also, studies on mechanism(s) through which rejection can happen after COVID-19, as well as immunosuppressive therapy during and subsequent to COVID-19 in transplant recipients is urgently needed.

Availability of data and materials: Pubmed database, ((kidney transplant recipient[Title/Abstract]) OR (kidney allograft recipient[Title/Abstract]) OR (kidney transplantation[Title/Abstract]) OR (kidney allograft rejection[Title/Abstract])) AND ((COVID-19[Title/Abstract]) OR (SARS-CoV-2[Title/Abstract])).

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Conflicts of interest
There are no conflicts of interest.

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