Coronavirus-19 infection in kidney transplant recipients: A comprehensive review

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ABSTRACT

The COVID-19 pandemic has disrupted health care across the globe. Since the beginning of the pandemic, there have been substantial changes in the approach toward kidney transplantation and management of the virus in transplant recipients. Chronic immunosuppression and comorbidities in renal transplant recipients place them at risk during the pandemic. Data on the risk factors, presentation, and management of kidney transplant patients have become more robust over time. Relevant data on this topic was procured and synthesized with the aid of a comprehensive Medline search on all published studies that investigated COVID-19 infection in kidney transplant recipients. This comprehensive review summarizes the current literature on the epidemiology, clinical features, complications, graft outcomes, and current management of COVID-19 infection in kidney transplant recipients. We further summarize published literature on immunization in kidney transplant recipients.

INTRODUCTION

In December 2019, the Municipal Health Commission in Wuhan, China, reported its first cases of a viral pneumonia that would later be attributed to severe acute respiratory syndrome-coronavirus2 (SARS-CoV-2). Since the virus has reached global pandemic proportions, with recurrent waves of increasing cases owing to new variants of the virus. Many organ transplant centers around the world initially stopped doing transplants due to a variety of risks, including but not limited to the risk of transmission to healthy living donors, concern for donor-to-recipient transmission, and limited available COVID testing. Since the first case report of COVID-19 in a kidney transplant patient in China was published in March 2020, researchers have been working to gather, analyze, and share knowledge.

METHODOLOGY

A literature search was performed using PubMed databases to identify relevant English language articles published from December 2019 to July 2021. Search terms included COVID-19, coronavirus, SARS coronavirus 2, 2019-nCoV, SARS-CoV-2, SARS-CoV, and transplantation. We divided our referenced studies into three categories: case reports consisting of one patient, small-to-medium-sized cohorts consisting of under 100 patients, and large, usually multicenter, cohorts consisting of over 100 patients. We focused on compiling demographic information, risk factors, and clinical outcomes from patients worldwide.

POPULATION OVERVIEW

The proportion of confirmed COVID-19 (with reverse transcription-polymerase chain reaction testing via nasopharyngeal swab) among kidney transplant patients has been reported to be from 1.42 to 16% among multicenter cohort studies. Table 1 describes the patient characteristics of the reviewed studies. The cohorts were mostly males in their 50s–60s. The most common patient comorbidity was...
reported to be hypertension, consistent across case reports, medium-sized studies, and multicenter cohorts. Diabetes and obesity were also commonly reported comorbidities. These patient characteristics are similar to those in the general population, which are mostly male,[9,10] advanced in age and with hypertension, obesity, and diabetes as common comorbidities.[11,12] The age of transplant at the time of COVID-19 infection or median transplant vintage was 48, 66, and 72 months among case studies, medium-sized studies, and multicenter cohorts, respectively.

CLINICAL PRESENTATION

Patients in the general population most commonly present with fever, followed by cough, dyspnea, and myalgia or fatigue.[1] Similar patterns of presentation were seen in the kidney transplant recipient population, described in Table 2. It appears that among kidney transplant patients with COVID-19, patients also frequently complain of diarrhea and other gastrointestinal symptoms on presentation; 23%, 27%, and 35% of patients reported with diarrhea among case reports, medium-sized reports, and multicenter cohorts, respectively. This presentation could be influenced by the usage of mycophenolate mofetil (MMF), a frequently prescribed immunosuppressant with a known side effect of diarrhea. Diarrhea in the general population has been reported to be a presenting symptom in between 3 and 10.4% of patients among more recent meta-analyses.[1,9,13]

DISEASE COURSE AND CLINICAL OUTCOMES

In the kidney transplant population, considerable proportions of those who had contracted SARS-CoV-2 developed an acute kidney injury (AKI). Among 52 case reports reviewed, 63% of patients had been diagnosed with an AKI during their hospitalization. Among medium-sized and multicenter cohorts, the median proportion of patients who had developed an AKI was 51% and 44%, respectively. This is in stark comparison to renal manifestations in the general population, of which studies have reported 0.5%–7% of COVID-19 cases developing an AKI.[1,14,15] This highlights our population’s increased vulnerability to kidney insult.

Among medium-sized and multicenter cohort studies, median of 20% and 21% of kidney transplant patients with COVID-19, respectively, succumbed to the disease. Rates of intensive care unit admission among kidney transplant patients were noted to be 21%–27%. Table 2 describes the disease course and clinical outcomes for kidney transplant patients with SARS-CoV-2 infection.

There are four reported cases of graft loss and two cases of de novo chronic antibody-mediated allograft rejection following SARS-CoV-2 infection among kidney transplant patients.[16-19] Of the four graft losses, two had a history of graft rejection prior to COVID-19 and a decreased baseline

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**Table 1: Patient characteristics and symptoms on presentation**

| Type of Study | Age (years, median, (IQR)) | Diabetes mellitus (DM), % | Hypertension (HTN), % | Heart disease (Heart Dx), % | Lung disease (Lung Dx), % | N/V | Diarrhea | Fever | Myalgia | Cough | Dyspnea |
|---------------|-----------------------------|---------------------------|-----------------------|-----------------------------|---------------------------|-----|----------|-------|--------|-------|---------|
| Case reports (52), n (%) | 49 (36-56.5) | 64% (46-75) | 40% (36-56) | 16% (8-35) | 8% (3-16) | 12% (7-21) | 15% (13-18) | 48 (15-12.5) | 76% (65-92) | 70% (70-80) | 75% (70-80) | 75% (70-80) |
| Medium-sized (63), n (%) | 53 (47-58) | 73% (60-91) | 73% (60-91) | 30% (21-40) | 30% (19-43) | 12% (7-21) | 15% (13-18) | 48 (15-12.5) | 76% (65-92) | 70% (70-80) | 75% (70-80) | 75% (70-80) |
| Multi-center (15), n (%) | 60 (57.4-51.4) | 86% (83-91) | 65% (57.4-51.4) | 27% (20-33) | 27% (20-33) | 12% (7-21) | 15% (13-18) | 48 (15-12.5) | 76% (65-92) | 70% (70-80) | 75% (70-80) | 75% (70-80) |

DM = Diabetes mellitus, HTN = Hypertension, IQR = Interquartile range, N/V = Nausea/vomiting.
glomerular filtration rate. Further large volume studies may reveal if the graft outcomes in patients with graft dysfunction prior to COVID-19 are different from recipients with healthy graft function. *De novo* anti-donor-specific antibodies have been reported following SARS-CoV-2 infection.[20]

Predictors of mortality among kidney transplant patients with SARS-CoV-2 infection were generally similar to those of the general population. In factors specific to kidney transplant recipients, shorter span of time between transplant and COVID-19 infection, deceased donor transplant, diabetic etiology of end-stage renal disease, and previous antirejection therapy were associated with increased mortality.[6,21,22] Active cytomegalovirus coinfection and bacterial coinfections were also shown to complicate and worsen the prognoses of kidney transplant patients.[23]

### IMMUNOSUPPRESSION MODIFICATION AND OTHER TREATMENTS

Immunosuppression regimens for kidney transplant patients frequently consist of a combination of calcineurin inhibitors (CNIs), azathioprine, mycophenolic acid/MMF (MPA/MMF), mammalian target of rapamycin-inhibitors, prednisone, and belatacept.[24] The combination most frequently seen in case reports and cohort studies included tacrolimus, mycophenolate, and prednisolone. In the management of COVID-19 in kidney transplant patients, MPA/MMF was discontinued in most cases due to its implications in suppressing the response of T-lymphocytes needed to mount an immune response to SARS-CoV-2.[25] Withdrawal of MPA/MMF was seen in 73% of case reports and a median of 88% and 74% in medium-sized and multicenter cohorts, respectfully. The withdrawal of a CNI was reported in 33% of case studies, a median of 50% in medium-sized cohorts, and a median of 23% in multicenter cohorts. More frequently, it was found that in patients who received anti-COVID-19 therapeutics, the tacrolimus doses had to be adjusted due to drug–drug interaction.[26-28]

In the treatment of COVID-19 in kidney transplant patients, reports of use of tocilizumab,[29-37] remdesivir,[38] low-dose methylprednisolone,[39] convalescent plasma therapy,[40-42] colchicine,[43] and favipiravir have been published.[36,44] However, most of these positive outcomes were observed in either case studies or small cohorts, and the use of any of these treatments should be considered on a case-by-case basis. Table 3 describes the reported frequency of immunosuppression regimen modification and treatment attempts among kidney transplant patients with COVID-19.

In kidney transplant patients, there have been multiple reports of limited immune response to the SARS-CoV-2 vaccine. Investigators have reported 89%–98% of kidney transplant recipients are seronegative after their first dose,[45-47] and 52%–94% remain seronegative after their second dose.[46,48-50] Table 4 describes the articles that have been published investigating immunological responses in vaccinated kidney transplant patients.

The limitations of our study include our use of descriptive studies comprising varied cohorts, which do not enable us to make any statements on causation. Furthermore, we must consider that we lack results from the era of unavailable to limited testing during the pandemic. It is difficult to compare patient outcomes holistically, as many patients...
who died may not have been tested, and only patients who were fit enough to go to access testing were included. Outcomes due to changes in immunosuppression regimens are largely unstudied and warrant investigation. Finally, our data is largely from the prevaccination era. Studies from the post-vaccination era are awaited.

CONCLUSION

As COVID-19 and its underlying virus become more understood, our ability to better protect our kidney transplant patients grows. We must continue to contribute to the evolving literature and clinical guidelines available on the treatment of COVID-19.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients with infected with 2019 novel coronavirus in Wuhan, China. Lancet Lond Engl 2020;395:497-506.
2. Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DD, Mishra S, et al. Genomics and epidemiology of a novel SARS-CoV-2 lineage in Manaus, Brazil. Science 2021;372:815-21. [doi: 10.1126/science.abh2644].
3. Boyarsky BJ, Po-Yu Chiang T, Werbel WA, Durand CM, Avery RK, Getzin SN, et al. Early impact of COVID-19 on transplant center practices and policies in the United States. Am J Transplant 2020;20:1809-18.
4. Jager KJ, Kramer A, Chesnaye NC, Couchoud C, Sánchez-Alvarez JE, Garneata L, et al. Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. Kidney Int 2020;98:1540-4.
5. Favà A, Cucchiari D, Monterro N, Toapanta N, Centellas FJ, Vila-Santandreu A, et al. Clinical characteristics and risk factors for severe COVID-19 in hospitalized kidney transplant recipients: A multicentric cohort study. Am J Transplant 2020;20:3030-41.
6. Thauvat O, Legeai C, Anglicheau D, Coutzi L, Blancho G, Hazzan M, et al. IMPACT of the COVID-19 epidemic on the morTality of kidney transplant recipients and candidates in a French Nationwide registry sTudy (IMPANT). Kidney Int 2020;98:1568-77.
7. Azzi Y, Parides M, Alani O, Loaute-Campos P, Bartash R, Forest S, et al. COVID-19 infection in kidney transplant recipients at the epicenter of pandemics. Kidney Int 2020;98:1559-67.
8. Zimmerman A, Rogers R, Tan CS, Pavlakis M, Bodziak K, Cardarelli F, et al. Expected the unexpected: COVID-19 in Kidney Transplant Recipients within United Network for Organ Sharing Region 1. Transpl Int 2020;33:1843-4.
9. Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol 2020;92:577-83.
10. Abate BB, Kassie AM, Kassaw MW, Aragie TG, Masresha SA. Sex difference in coronavirus disease (COVID-19): A systematic review and meta-analysis. BMJ Open 2020;10:e040129.
11. Garg S. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 – COVID-NET, 14 States, March 1-30, 2020. MMWR Mortal Mortal Wkly Rep 2020;69:458-64.
12. Zhang JJ, Lee KS, Ang LW, Leo YS, Young BE. Risk factors for severe disease and efficacy of treatment in patients infected with COVID-19: A systematic review, meta-analysis, and meta-regression analysis. Clin Infect Dis 2020;71:12199-206.
13. D’Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea during COVID-19 infection: Pathogenesis, epidemiology, prevention, and management. Clin Gastroenterol Hepatol 2020;18:1663-72.
14. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395:507-13.
15. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
16. Bennett D, Franchi F, De Vita E, Mazzei MA, Volterrani L, Disanto MG, et al. SARS-CoV-2 in pleural fluid in a kidney transplant patient. Postgrad Med 2021;133:540-3.
17. Webb C, Davidson B, Jones ESW, Wearne N, Chetty DR, Blom D, et al. COVID-19-associated graft loss from renal infarction in a kidney transplant recipient. Kidney Int Rep 2021;6:1166-9.
18. Trujillo H, Fernández-Ruiz M, Gutiérrez E, Sevillano Á, Caravaca-Foná F, Morales E, et al. Invasive pulmonary aspergillosis associated with COVID-19 in a kidney transplant recipient. Transpl Infect Dis 2021;23:e13501.
19. Anandh U, Gowrishankar S, Sharma A, Salama A, Dasgupta I. Kidney transplant dysfunction in a patient with COVID-19 infection: Role of concurrent Sars-Cov 2 nephropathy, chronic rejection and vitamin C-mediated hyperoxalosis: Case report. BMC Nephrol 2021;22:91.
20. Abuzeineh M, Tariq A, Rosenberg A, Brennan DC. Chronic active antibody-mediated rejection following COVID-19 infection in a kidney transplant recipient: A case report. Transplant Proc 2021;53:1202-6.
21. Hilbrands LB, Duivenvoorden R, Vart P, Franssen CF, Hemmelder MH, Jager KJ, et al. COVID-19-related mortality in kidney transplant and dialysis patients: Results of the ERACOA collaboration. Nephrol Dial Transplant 2020;35:1973-83.
22. Crespo M, Pérez-Sáez MJ, Redondo-Pachón D, Llinàs-Mallo I, Montero MM, Villar-García J, et al. COVID-19 in elderly kidney transplant recipients. Am J Transplant 2020;20:2883-9.
23. Pierrotti LC, Reusing Junior JO, Freire MP, Barros Machado DJ, Moreira RM, Ventura CG, et al. COVID-19 among kidney-transplant recipients requiring hospitalization: Preliminary data and outcomes from a single-center in Brazil. Transpl Int 2020;33:1837-42.
24. Lim MA, Kohli J, Bloom RD. Immunosuppression for kidney transplantation: Where are we now and where are we going? Transplant Rev (Orlando) 2017;31:10-7.
25. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology 2000;47:85-118.
26. Bartiroimo M, Borch B, Botta A, Bagalà A, Lugli G, Tili M, et al. Threatening drug-drug interaction in a kidney transplant patient with coronavirus disease 2019 (COVID-19). Transl Infect Dis 2020;22:e13286.
27. Kim Y, Kwon O, Paek JH, Park WY, Jin K, Hynn M, et al. Two distinct cases with COVID-19 in kidney transplant recipients. Am J Transplant 2020;20:2269-75.
28. Oguz EG, Atligan KG, Cimen SG, Sahin H, Selen T, Ebinc FA, et al. COVID-19 infection in a kidney transplant recipient-special emphasis on pharmacokinetic interactions: A case report. World J Transplant 2020;10:365-71.
29. Pérez-Sáez MJ, Blasco M, Redondo-Pachón D, Ventura-Aguirar P, Bada-Bosch T, Pérez-Flores I, et al. Use of tocilizumab in kidney transplant recipients with COVID-19. Am J Transplant 2020;20:3182-90.
30. Bodro M, Cofan F, Ríos J, Herrera S, Linares L, Marcos MA, et al. Invasive pulmonary aspergillosis associated with COVID-19 in a kidney transplant recipient. Transpl Infect Dis 2020;22:e13326.
31. Gautier-Vargas G, Baldacini C, Benotmane I, Keller N, Perrin P, Moulin B,
et al. Rapid resolution of cytokine release syndrome and favorable clinical course of severe COVID-19 in a kidney transplant recipient treated with tocilizumab. Kidney Int 2020;98:508-9.

34. Mella A, Mingozzi S, Gallo E, Lavacca A, Rossetti M, Clari R, et al. Case series of six kidney transplanted patients with COVID-19 pneumonia treated with tocilizumab. Transpl Infect Dis 2020;22:e13348.

35. Trujillo H, Caravaca-Fontán F, Sevillaño A, Gutiérrez E, Fernández-Ruiz M, López-Medrano F, et al. Tocilizumab use in kidney transplant patients with COVID-19. Clin Transplant 2020;34:e14072.

36. Thammathiwat T, Tungsanga S, Tiankanon K, Torvorapanit P, Chumpangern W, Udomkarnjananun S, et al. A case of successful treatment of severe COVID-19 pneumonia with favipiravir and tocilizumab in post-kidney transplant recipient. Transpl Infect Dis 2021;23:e13388.

37. Fontana F, Alfano G, Mori G, Amurri A, Tei L, Ballestri M, et al. COVID‑19 pneumonia in a kidney transplant recipient successfully treated with tocilizumab and hydroxychloroquine. Am J Transplant 2020;20:1902-6.

38. Meshram HS, Kute VB, Patel H, Banerjee S, Navadiya V, Desai S, et al. Feasibility and safety of remdesivir in SARS-CoV2 infected renal transplant recipients: A retrospective cohort from a developing nation. Transpl Infect Dis 2021;23:e13629.

39. Tanaka R, Kakuta Y, Tsutahara K, Nakagawa M, Ichimaru N, Sakaguchi K, et al. Successful recovery from coronavirus disease 2019 in a living kidney transplant recipient using low-dose methylprednisolone. IJU Case Rep 2020;4:22‑4.

40. Naeem S, Gohh R, Bayliss C, Farmakiotis D, Merhi B, et al. Successful recovery from COVID-19 in three kidney transplant recipients who received convalescent plasma therapy. Transpl Infect Dis 2021;23:e13451.

41. Trimarchi H, Giannserra R, Lampo M, Monkowski M, Lodolo J, Eculizumab, SARS-CoV-2 and atypical hemolytic uremic syndrome. Clin Kidney J 2020;13:739-41.

42. Jiang J, Miao Y, Zhao Y, Lu X, Zhou P, Zhou X, et al. Convalescent plasma therapy: Helpful treatment of COVID-19 in a kidney transplant recipient presenting with severe clinical manifestations and complex complications. Clin Transplant 2020;34:e14025.

43. Nozato S, Ito A, Terashima K, Nozato Y, Yoshii Y, Seki K, et al. Successful treatment of COVID-19 with colchicine in a kidney transplant recipient. QJM 2021;114:197-9.

44. Tatar E, Karatas M, Bozaci I, Ari A, Acar T, Simsek C, et al. Intravenous immunoglobulin and favipiravir treatment for a kidney transplant patient with severe COVID-19 pneumonia. Transfus Apher Sci 2020;59:102904.

45. Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, Braun-Parvez L, et al. Weak anti-SARS-CoV-2 antibody response after the first injection of an mRNA COVID-19 vaccine in kidney transplant recipients. Kidney Int 2021;99:1487-9.

46. Chavarot N, Ouedrani A, Marion O, Leruez-Ville M, Vilain E, Baaziz M, et al. Poor anti-SARS-CoV-2 humoral and t-cell responses after 2 injections of mRNA vaccine in kidney transplant recipients treated with belatacept. Transplantation 2021;105:e94-5.

47. Yi SG, Knight RJ, Graviss EA, Moore LW, Nguyen DT, Ghobrial RM, et al. Kidney transplant recipients rarely show an early antibody response following the first COVID-19 vaccine administration. Transplantation 2021;105:e72-3.

48. Husain SA, Tsapepas D, Paget KF, Chang JH, Crew RJ, Dube GK, et al. Post-vaccine anti-SARS-CoV-2 spike protein antibody development in kidney transplant recipients. Kidney Int Rep 2021;6:1699-700.

49. Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, Braun-Parvez L, et al. Low immunization rates among kidney transplant recipients who received 2 doses of the mRNA-1273 SARS-CoV-2 vaccine. Kidney Int 2021;99:1498-500.

50. Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atama A, et al. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: A prospective cohort study. Clin Microbiol Infect 2021;27:1173.e1-4.

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