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CASE REPORT

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Clinical outcomes of post-renal transplant patients with COVID-19 infection in the ICU: A single-center case series

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Abstract

Most of the post-renal transplant patients are taking immunosuppressive medications, including calcineurin inhibitors, anti-proliferative agents, and steroids. This case series highlights the clinical characteristics and outcomes of eight post-renal transplant patients with severe COVID-19 infection admitted to the intensive care unit.

KEYWORDS

acute kidney injury, COVID-19 infection, end-stage renal disease, hypertension, immunosuppression, renal transplant

1 | BACKGROUND

Coronavirus disease (COVID-19) started in China as a severe pneumonia of unknown cause in late 2019 and quickly spread throughout the world with human-to-human transmission. COVID-19 was declared a pandemic in the first quarter of 2020 by the World Health Organization (WHO)[1] and has caused a significant mortality and financial resources worldwide. The pandemic is far from being over and has compromised even the most developed countries' healthcare systems. There are various risk factors for getting severe COVID-19 infection, such as patients' age and comorbidities including diabetes, cardiovascular and chronic respiratory disorders.[2-4] However, the role of immunosuppression therapy is still not

clear.[5] Use of the immunosuppressant medication in post-renal transplant patients may increase the risk of various viral infections.[6]

Adequate literature is not available from the region regarding the impact of COVID-19 infection in post-renal transplant patients, whereas the international literature is limited to a case series with contrast findings and conclusions.[7]

This case series explores the occurrence of severe COVID-19 infection in renal transplant recipients admitted to the intensive care unit, their risk factors, severity, course of the disease, and clinical outcomes.

2 | PATIENT AND METHODS

We enrolled only the severe cases of post-renal transplant patients diagnosed with COVID-19 infection with a polymerase chain reaction test (PCR) who were admitted to the intensive care unit (ICU) of our hospital from March 1 to September 30, 2020. All patient's demographic data, number and type of comorbidities, type and timing of the transplant, current patient medications, the severity of the disease, sepsis markers, acute kidney injury, renal replacement therapy requirements, secondary infections, ventilatory requirements, and ventilator days need of vasopressors and outcomes were recorded retrospectively from the patients' electronic data files.

3 | RESULTS

A total of eight post-renal transplant patients with COVID-19 infection were admitted to the intensive care unit during the study period. Five of the eight patients were female. The most common comorbid condition among our cohort (eight patients) was hypertension. Four of our patients had type 2 diabetes mellitus. Another four patients had a previous history of chronic respiratory disease, including asthma or chronic obstructive pulmonary disease (COPD). Coronary artery disease and hyperlipidemia were present in four and one patients, respectively (Table 1). Five patients had a history of renal transplant from living-related donors, while three patients had received their kidneys from cadaveric donors. Post-renal transplant period ranged from 4 to 16 years with a mean of 8.6 years (Table 2).

Out of the eight patients, seven presented with fever (87.5%), four with shortness of breath (50%), and five with hypoxia (62.5%). Their laboratory findings showed a frequent occurrence of lymphopenia (87.5%), low mean serum albumin (29 g/L), and high mean procalcitonin level (1.6 ng/ml) on admission to the ICU. Septic markers, including COVID-19 severity markers, (C-reactive protein, ferritin, D-dimer, and fibrinogen) were significantly elevated. The mean APACHE score was 13.88 with a range of 6–20 (Table 2). Only one of the eight patients had a positive cytomegalovirus (CMV) viremia with of CMV PCR level 12543 IU/ml.

At the time of COVID-19 infection, all patients had been taking immunosuppressant medications in the form of (tacrolimus or cyclosporin plus mycophenolate mofetil or azathioprine) and small dose of prednisolone. The anti-proliferative agents (mycophenolate mofetil and azathioprine) were discontinued whereas the calcineurin inhibitors (tacrolimus and cyclosporin) were reduced in all eight patients during COVID-19 infection. Steroid doses were increased during COVID-19 infection and ICU stay. Antiviral treatment with hydroxychloroquine was used in seven patients (87.5%), azithromycin in seven patients (87.5%), oseltamivir in five patients (62.5%), and lopinavir-ritonavir in three patients (37.5%). In addition, tocilizumab was used in five patients only (62.5%). Secondary bacterial infection occurred in three patients only, and three patients required invasive ventilatory support. Mean mechanical ventilation days in the three intubated patients were 20.19 with a range of 14–25 days (Table 3). Only four patients required vasopressors to maintain their hemodynamics. All the eight patients developed acute renal allograft dysfunction due to sepsis. None of our patients had renal

TABLE 1 Patients demography and comorbidities

Patient	Gender	Age (Years)	Diabetes mellitus	Hypertension	Coronary artery disease	Chronic respiratory disease	Hyperlipidemia
1	Female	61	No	No	No	Yes	No
2	Female	35	No	Yes	No	No	No
3	Female	53	No	Yes	No	Yes	Yes
4	Male	54	Yes	Yes	No	No	No
5	Male	63	Yes	Yes	Yes	No	No
6	Female	61	YES	YES	NO	YES	NO
7	Male	55	NO	YES	NO	NO	NO
8	Female	51	YES	YES	YES	YES	NO
	5:Female 3: Male	Mean = 54.1	Yes:4 (50%)	Yes:7 (87.5%)	Yes:2 (25%)	Yes:4 (50%)	Yes:1 (12.5%)

TABLE 2 Renal transplant details and markers

Patient number	Years of transplant	Type of renal transplant	APACHE2 score	Ferritin levels	D-dimer	Fibrinogen	C-reactive protein
1	4	Live related donor	8	587	0.85	4.8	165.4
2	11	Deceased donor	12	367	0.81	3.6	30
3	5	Live related donor	6	693	1.77	8.2	287.6
4	5	Deceased donor	11	1398	0.55	4.3	76.6
5	6	Deceased donor	25	335	N	5	295.5
6	9	Live related donor	15	1010	0.91	4.8	42
7	16	Live related donor	14	386.00	1.03	4.8	156.7
8	13	Live related donor	20	1467	1.07	5	104.4
	Mean=8.6 years	Live related donor = 5 Deceased donor = 3	Mean:13.88	Elevated	Elevated	Elevated	Elevated

TABLE 3 Descriptive and outcome parameters

Patient number	Acute kidney injury (AKI) required RRT	Secondary infection	Intubation	Mechanical ventilation days	Total ICU stay (days)	Mortality
1	No	Yes	Yes	14	20	No
2	No	No	No	0	2	No
3	Yes	Yes	Yes	24	25	Yes
4	Yes	Yes	Yes	25	64	No
5	No	Yes	No	0	19	No
6	No	No	No	0	3	No
7	No	No	No	0	8	No
8	YES	YES	NO	0	41	NO
	Required RRT: 3 (37.5%)	Yes:5(62.5%) No:3(37.5)	Yes:3(37.5%) No:5(62.5%)	Mean:20.19	Mean:22.75	Yes:1(12.5%)

Abbreviation: RRT, renal replacement therapy.

transplant rejection and only three of them (37.5%) received renal replacement therapy in the form of hemodialysis (Table 3). One of these patients died while staying in the ICU giving a mortality of 12.5% in our patient series. (Table 3). Five patients (62.5%) with acute renal allograft dysfunction had a renal recovery, while two recipients (25%) became dialysis-dependent at 30 days following the COVID-19 infection.

4 | DISCUSSION

Post-renal transplant patients are hypothetically at a higher risk of acquiring COVID-19 infection due to various reasons, including immunosuppressive medications, steroid therapy, and malnutrition.[6] A study conducted in Europe from the French and Spanish registry showed an average infection rate of 14 in 1000 renal transplants at risk.[8] Elias et al identified obesity, diabetes mellitus, and chronic pulmonary diseases as some of the risk factors of COVID-19 infection in renal transplant recipients.[9] Elhadedy et al[10] also found that hypertension and diabetes mellitus were the most common risk factors for COVID-19 infection in this group of patients. The most common risk factors or comorbidity were hypertension, diabetes mellitus, and chronic pulmonary disease in our cohort. All our patients had undergone kidney transplantation many years back with mean duration of 8.4 years, and most of them received the kidney from live-related donors. This contrasted with most of the literature, which states that cadaveric renal transplants and recently transplanted renal recipients were at a higher risk of acquiring COVID-19 infection.[9,10] We also had a higher number of female patients, which is in contrast to the available literature.[9,10] Similarities to literature include having very high inflammatory and sepsis markers, including ferritin, C-reactive protein, fibrinogen, and D-dimers.

Immunosuppressant medications were continued in lower doses in kidney transplant recipients during COVID-19 infection. In our cohort, we discontinued the anti-proliferative agents (mycophenolate mofetil and azathioprine), subsequently reduced or stopped the calcineurin inhibitors (tacrolimus and cyclosporin), and given a higher dose of steroids in all eight patients. In a registry-based observational study from France that included 279 renal transplant patients, the calcineurin inhibitors were stopped in 28.7% of patients and antimetabolites in 70.8% of patients.[11]

Basically, the management of kidney transplant with COVID-19 infection is extrapolated from evidence obtained from treating other life-threatening infections, which involves reducing or stopping immunosuppression. Various studies reported that elective withdrawal of calcineurin inhibitors (CNI) increases the risk of acute allograft rejection more than withdrawal of mycophenolate mofetil.[12,13] Moreover, Carbajo-Lozoya et al[14] suggested that CNI agents might inhibit the growth and replication of coronaviruses. These findings may support the continued use of CNI agents while reducing or withholding anti-proliferative drugs (mycophenolate and azathioprine) in transplant recipients with COVID-19 infection. Reintroduction of antimetabolite agents may be delayed for up to 2 weeks after discharge or cure from COVID-19 infection. CNI Levels should be frequently monitored and minimized during active viral infection and drug-drug interaction. It is well known that withdrawal of one of the immunosuppressive agents necessitate increasing the dose of steroids to prevent renal allograft rejection. Furthermore, high doses of steroids are sometimes used in the critically ill patients for other reasons.

Acute kidney injury and the requirement of renal replacement therapy is also common with COVID-19 infection. A study from England reported that 57% of post-renal transplant patients with COVID-19 required renal replacement therapy.[15] Elhadedy et al reported that 26% of their patients required hemodialysis. In our patient's series, three patients (37.5%) required renal replacement therapy in the form of hemodialysis. These three patients have a baseline chronic renal allograft dysfunction before COVID-19 infection.

Around 37.5% of our cohort required intubation and invasive ventilation. Elias et al[9] reported that 22% of their patients required invasive ventilation. Banerji et al[15] reported one (14%) out of their seven patients required invasive ventilation. Mechanical ventilation was required for around 30% in the French registry.[11]

Available literature describes that post-renal transplant patients with COVID-19 infection had higher mortality than the general population, ranging from 14 to 24%.[9,15] In our case series, mortality was 12.5% as one of our eight patients died due to disease progression and complications. Whereas the 30-day mortality rate in the French study that included 279 renal transplant patients was 22.8% with the increasing age and cardiovascular disease as independent risk factors for mortality.[11]

5 | CONCLUSION

Post-renal transplant patients have high chances of complications with COVID-19 infection due to their immunosuppressed status and related comorbidities. They also have a significant risk of developing acute kidney injury and severe pneumonia requiring invasive ventilation. In our case series, hypertension was a common risk factor, and female patients were more significant in number. Most of the patients had received the transplanted kidneys years ago, and all of them were taking immunosuppressive medications, including steroids. Complications of disease and mortality among these critical patients were high compared to immunocompetent patients.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

NS, MYK, MAW, DCA, MO, AO, SBJ, SB, ZN, ASM, MSE, AJN: Data Collection, Literature Search, Manuscript Preparation. MAA: Manuscript Final Edit. All authors read and approved the final manuscript.

ETHICAL APPROVAL

The article describes a case series. Therefore, no additional permission from our Ethics Committee was required.

CONSENT FOR PUBLICATION

The consent for publication was obtained.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

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